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TITLE OF STUDY: A Randomized, Double-Blind, Placebo-Controlled 52-Week Study to Assess Adverse Events of Special Interest in Adults with Active, Autoantibody-Positive Systemic Lupus Erythematosus Receiving Belimumab

STUDY SPONSOR:

Human Genome Sciences, Inc.
14200 Shady Grove Road
Rockville, Maryland 20850

Confidentiality

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*A Summary of Modifications document which provides a detailed list of changes for the amendment/addendum is available upon request.

Investigator Agreement

I will provide copies of the protocol, any subsequent amendments and access to all information furnished by the sponsor to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational study agent and the study protocol. I agree to conduct this clinical trial according to the protocol described herein, except when mutually agreed to in writing with the sponsor. I also agree to conduct this study in compliance with Good Clinical Practice (GCP) standards as defined by the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice, all applicable national, state, and local regulations, as well as the requirements of the appropriate Institutional Review Board/Independent Ethics Committee and any other institutional requirements.

Principal Investigator:

_____

Signature *Date*

_____

Name (please type or print)

_____

Institution

_____

Address

Study Synopsis

Study Number: HGS1006-1113

Title of the Study: A Randomized, Double-Blind Placebo-Controlled 52-Week Study to Assess Adverse Events of Special Interest in Adults with Active, Autoantibody-Positive Systemic Lupus Erythematosus Receiving Belimumab

Objectives:

The objectives of this study are to evaluate the following in adult SLE subjects receiving belimumab plus standard therapy versus subjects receiving placebo plus standard therapy:

- Mortality and adverse events of special interest over 1 year (52 weeks).
- Corticosteroid reduction during Weeks 40-52.

Diagnosis & Inclusion Criteria: Subjects enrolled in the study must meet the following inclusion criteria:

1. Males or females ≥ 18 years.
2. Have a diagnosis of SLE, refer to ACR revised criteria for the classification of SLE (Appendix 1) as a guide for diagnosis of SLE.
3. Active, autoantibody positive SLE (autoantibody positive is defined as the presence of ANA or anti-dsDNA antibodies).
4. Are on a SLE treatment regimen consisting of any of the following medications (alone or in combination):
   - Corticosteroids
   - Other immunomodulatory agents including methotrexate, azathioprine, leflunomide, mycophenolate (including mycophenolate mofetil, mycophenolate mofetil hydrochloride, and mycophenolate sodium), calcineurin inhibitors (eg, tacrolimus, cyclosporine), sirolimus, oral cyclophosphamide, 6-mercaptopurine, or thalidomide.
   - Anti-malarials [eg, hydroxychloroquine, chloroquine, quinacrine (mepacrine)]
5. A female subject is eligible to enter the study if she is:
   - Not pregnant or nursing;
   - Of non-childbearing potential defined as:
     - pre-menopausal females with a documented tubal ligation, hysterectomy, documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion, or documented bilateral oophorectomy or
     - postmenopausal defined as 12 months of spontaneous amenorrhea with an appropriate clinical profile [e.g., > 45 years, in the absence of hormone replacement therapy or other cause for amenorrhea]; in questionable cases obtain a blood sample for follicle stimulating hormone (FSH) and estradiol

simultaneously to confirm. Diagnostic levels for FSH and estradiol vary by specific laboratories/assays;

- OR is of child-bearing potential with negative pregnancy test as determined by urine human chorionic gonadotrophin (hCG) test at screening and urine hCG test prior to dosing AND
  - Agrees to use one of the contraception methods listed in the protocol (see Section 4.3) for 2 weeks prior to the day of dosing to sufficiently minimize the risk of pregnancy at that point. Female subjects must agree to use contraception until 16 weeks following the last dose of study agent.
  - OR has only same-sex partners, when this is her preferred and usual lifestyle.

6. Have the ability to understand the requirements of the study, provide written informed consent (including consent for the use and disclosure of research-related health information), and comply with the study data collection procedures [including annual contacts from Years 2 through 5 (Week 260) to assess mortality and malignancy].

Exclusion Criteria: Subjects will be excluded from participating in the study if they meet any of the following exclusion criteria:

1. Have received any prior treatment with belimumab, either as a marketed product or as an investigational agent.
2. Have received treatment with B cell targeted therapy (eg, rituximab, other anti-CD20 agents, anti-CD22 [epratuzumab], anti-CD52 [alemtuzumab], BLyS-receptor fusion protein [BR3], TACI-Fc, anti-BAFF [LY2127399]) within 364 days of Day 0.
3. Have received any of the following within 90 days of Day 0:
   - Any biologic agent (eg, adalimumab, etanercept, infliximab, anakinra) other than B cell targeted therapy (see Exclusion Criterion 2).
   - Plasmapheresis.
4. Have received any of the following within 60 days of Day 0:
   - A non-biologic investigational agent.
5. Have received any of the following within 30 days of Day 0:
   - A live vaccine.
6. Have a history of malignant neoplasm within the last 5 years, except for adequately treated cancers of the skin (basal or squamous cell) or carcinoma in situ of the uterine cervix.
7. Have required management of acute or chronic infections, as follows:
   - Currently on any suppressive therapy for a chronic infection (such as tuberculosis, pneumocystis, cytomegalovirus, herpes simplex virus, herpes zoster and atypical mycobacteria).
   - Hospitalization for treatment of infection within 60 days of Day 0.
   - Use of parenteral (IV or IM) antibiotics (antibacterials, antivirals, anti-fungals, or anti-parasitic agents) within 60 days of Day 0.

8. Have severe lupus kidney disease (defined by proteinuria > 6 g/24 hour or equivalent using spot urine protein to creatinine ratio, or serum creatinine > 2.5 mg/dL), or have severe active nephritis requiring acute therapy, or have required hemodialysis or high-dose prednisone or equivalent (> 100 mg/day) within 90 days of Day 0.
9. Have severe active central nervous system (CNS) lupus (including seizures, psychosis, organic brain syndrome, cerebrovascular accident [CVA], cerebritis or CNS vasculitis) requiring therapeutic intervention.
10. Known HIV infection.
11. Current or history of hepatitis B or hepatitis C infection.
12. ***Only applicable to Lithuanian sites:***
    - Have hypogammaglobulinaemia (IgG <400 mg/dL) or a deficiency in immunoglobulin A (IgA <10 mg/dL).
    - Have had renal, stem cell/marrow or other major organ transplant.
    - Have a chronic infection or a history of recurrent infections, which in the opinion of the investigator poses a significant risk to the subject.
    - Have received cyclophosphamide via any route of administration within 90 days of Day 0.

Study Design and Schedule:

This is a global, multi-center, randomized, placebo-controlled study to evaluate adverse events of special interest in adults with active, autoantibody-positive systemic lupus erythematosus (SLE) treated with belimumab plus standard therapy vs placebo plus standard therapy. It was initially planned that approximately 5,000 subjects would be randomized to 1 of 2 treatment groups: belimumab 10 mg/kg (2,500 subjects) or placebo (2,500 subjects) plus standard therapies. Subseqent to the completion of 2 additional placebo-controlled trials, it was estimated based on data from all 5 of the completed Phase 2/3 trials that adverse event rates could be assessed with the same planned level of precision with a total sample size of 4,000 subjects. Consequently, a sample size reduction was proposed to and accepted by the FDA and EMA regulatory authorities.

Subjects will receive study agent (belimumab or placebo) on Days 0, 14, 28 and approximately every 28 days thereafter through Week 48 with a final visit conducted at Week 52. Subjects who discontinue treatment at any time during the 52-week study will be followed for mortality and malignancy including non-melanoma skin cancers (NMSC) at 1 year (through Week 52) and annually for Years 2 through 5.

Subject data will be collected at randomization and subsequently at approximately 28-day intervals for 52 weeks. Subjects will be assessed for malignancies including NMSC, serious infections, opportunistic infections and other infections of interest, selected serious psychiatric events, suicidality, and serious infusion and hypersensitivity reactions. All cause mortality will be reported. All other serious adverse events (SAEs), irrespective of causality, will also be recorded. Medical history will be collected on all subjects. Immunomodulatory agents used to treat SLE at baseline and during study, hospitalizations, and organ damage (SLICC/ACR Damage Index) will also be assessed through Week 52.

All subjects will have a follow-up visit performed approximately 4 weeks after the last dose of study agent. In the event that a subject withdraws consent to participate in the first year monthly study visits, an attempt should be made at the time of consent withdrawal to obtain consent to contact the subject at Week 52 and annually for Years 2 through 5 (Week 260) to assess mortality and malignancy (including NMSC).

Subjects may continue to receive their other SLE medications including corticosteroids, immunomodulatory agents and antimalarials; changes in these SLE medications during the trial will be permitted as clinically indicated. No concomitant biological therapies will be allowed during the 52-week study. In the event that the treating physician decides that a subject requires the addition of a biologic agent before Week 52, the subject is withdrawn from study agent treatment, but is followed on the study through Week 52 and annually for Years 2 through 5 (Week 260).

Following the 52-week study, all subjects will be contacted annually through Year 5 (Week 260) to assess mortality and malignancy (including NMSC).

At the end of the 52-week study, subjects who wish to continue treatment may be able to do so by being prescribed commercially available belimumab. If belimumab is not commercially available in a subject's country of participation, the subject may be able to receive belimumab under a separate continuation protocol. A separate informed consent will need to be provided for the continuation protocol.

An Independent Data Monitoring Committee (IDMC) will review unblinded safety data for this study on an ongoing basis until the data are locked and analyzed. The IDMC will include at least 3 physicians, and a statistician, none of whom are affiliated with the sponsor. The first IDMC meeting will review the data after approximately 500 subjects have been treated or 6 months from randomization of the first patient, whichever is first. After the initial review, the IDMC will continue to review the data approximately every 6 months. Events to be monitored during the safety review will include at a minimum all serious adverse events (including deaths, serious psychiatric events and serious infections), opportunistic infections (serious and nonserious) and other infections of interest, malignancies (including NMSC), and serious infusion and hypersensitivity reactions. Investigators and IRBs/IECs will be notified of the outcome of each IDMC meeting.

Endpoints and Statistical Analysis:

The main purpose of this study is to provide an evaluation of the difference in the rates of all prespecified AESI and all cause mortality between the belimumab and the placebo groups with a 2-sided 95% confidence interval (CI). SAEs will be analyzed descriptively only.

Safety Endpoints:

The table below describes the safety endpoints and measures collected in the study.

All-cause mortality
Serious Infections (including serious opportunistic infections and any event of TB or TB reactivation)
Non-serious opportunistic infections and other infections of interest (Appendix 2)
Malignancies (excluding NMSC)
Non-melanoma skin cancers
Psychiatric events suggesting serious mood disorders and anxiety
Suicidality (using C-SSRS; Appendix 4 and Appendix 5)
Serious Infusion and Hypersensitivity Reactions
All SAEs

Efficacy Endpoints:

The major efficacy endpoint is:

- Percent of subjects whose average prednisone (or equivalent) dose has been reduced by $\geq 25\%$ from baseline to ≤ 7.5 mg/day during Weeks 40 through 52 (in the subgroup of subjects receiving > 7.5 mg/day of prednisone (or equivalent) at baseline).

Other efficacy endpoints include:

- Use of immunomodulatory medications to treat SLE over 1 year.
- Number of hospitalizations per patient.
- Percent of patients hospitalized.

SLICC/ACR Damage Index will be recorded at baseline and at Week 52 to allow assessment of accrual of damage in subjects who may be followed in a subsequent study.

Sample Size Considerations:

The sample size is based on the feasibility of enrolling a large number of SLE subjects in a global trial that will provide a reasonable estimate for mortality and other AESI rates. Originally, the sample size was approximated at 5,000 subjects to be randomized (1:1 randomization; 2,500 per treatment group) to thereby allowing the difference in mortality rate between the belimumab- and placebo-treated groups to be established with a 95% CI of $\pm$ 0.46% (see Section 8.4 of the protocol).

Following completion of two additional placebo-controlled trials (each comprising 1 year of treatment), a revised mortality estimate based on data from all 5 of the completed 2/3 trials enabled the same level of precision (i.e., a 95% CI of $\pm$ 0.46%) for the difference in

mortality between placebo and belimumab to be achieved with 4,000 subjects. Consequently, a proposal to reduce the sample size from 5,000 to 4,000 subjects was accepted by regulatory authorities.

The randomization will be stratified for region (US/Canada vs Central America/South America/Mexico vs Europe/Australia/Israel vs Asia), SELENA SLEDAI score (≤ 9 vs ≥ 10), and steroid dose (≤7.5 mg/day vs >7.5 mg/day prednisone or equivalent).

Safety Analysis:

Mortality and AESI will be summarized descriptively using number and percentage of subjects and will be analyzed using an estimation paradigm. The difference in the rates of all prespecified AESI and all cause mortality, between the belimumab and the placebo groups will be evaluated with a 2-sided 95% CI. SAEs will be analyzed descriptively only. Deaths will also be described in detail, including, in the belimumab group, assessment of relationship to belimumab treatment. The frequency and rate of serious adverse events will be tabulated by MedDRA system organ class (SOC) and preferred term. The SAE rates may also be reported adjusted for subject years.

For all cause mortality, the hazard ratio (and its 95% CI) for belimumab vs placebo will be estimated using the Cox proportional hazard model, adjusted for baseline randomization factors. The time to death will be censored at the last follow-up by the end of the study for subjects who are alive.

Safety analyses will be performed using the As-Treated population, defined as all randomized subjects who receive a dose of study agent, grouped according to the actual treatment administered to the subject for more than 50% of the doses.

Analysis of Major Efficacy Endpoint:

The percent of subjects with average prednisone (or equivalent) dose that has been reduced by ≥ 25% from baseline to ≤ 7.5 mg/day during Weeks 40 through 52 will be compared between the belimumab and the placebo groups using a logistic regression model, adjusted for baseline prednisone (or equivalent) dose level, baseline SELENA SLEDAI score (≤ 9 vs ≥ 10), and region (US/Canada or Central America/South America/Mexico or Europe/Australia/Israel or Asia). The analysis will be performed on subjects who were using prednisone (or equivalent) at a dose > 7.5 mg/day at baseline and were in the intent-to-treat (ITT) population. In the analysis, all subjects who drop out and/or add new immunosuppressive agents before the Week 52 visit will be considered having no steroid reduction. However, switching immunomodulatory agents for toxicity reasons or lack of availability (eg, no longer manufactured or no longer reimbursed) is permitted and will not be imputed as no steroid reduction. To examine the robustness of the results, a sensitivity analysis of the steroid reduction may be performed without considering any information related to the use of new immunomodulatory agents.

Study Calendar:

See Section 6 for a calendar of study visits and assessments.

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List of Abbreviations

ACR	American College of Rheumatology
ADA	Anti-Drug Antibodies
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANA	Anti-nuclear antibody
Anti-dsDNA	Anti-double-stranded DNA
Anti-TNF	Anti-tumor necrosis factor
BAFF	B cell activating factor belonging to the THF family
BEL	Belimumab
BLyS	B lymphocyte stimulator
°C	degrees Celsius
CI	Confidence Interval
CMV	Cytomegalovirus
CRD	Controlled repeat dose
C-SSRS	Columbia-Suicide Severity Rating Scale
DNA	deoxyribonucleic acid
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
HGS	Human Genome Sciences
HIV	human immunodeficiency virus
HR	Hazard Ratio
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IUD	intrauterine device
IV	intravenous
Kg	kilogram
LOCF	last observation carried forward
MDD	major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	milliliter
NHL	non-Hodgkins lymphoma
NMSC	non-melanoma skin cancer
PGx	pharmacogenetics
PML	progressive multifocal leukoencephalopathy
PSRQ	possible suicidality related questionnaire
SAE	serious adverse event
SC	subcutaneous, subcutaneously

SELENA	Safety of Estrogen in Lupus National Assessment
SLE	systemic lupus erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SLICC	Systemic Lupus International Collaborating Clinics
SIR	standardized incidence ratio
SRI	SLE responder index
SWFI	sterile water for injection
TB	tuberculosis
TNF	tumor necrosis factor
US	United States
USAN/INN	United States adopted names/international nonproprietary name

1 Background

1.1 Disease Background Relevant to Clinical Study

SLE is a chronic debilitating autoimmune disease that primarily affects young women of childbearing age, although men, children and teenagers also can develop lupus. SLE is characterized by the presence of autoreactive B cells resulting in elevated levels of autoantibodies, which directly damage the body's cells and tissues or form immune complexes which cause inflammation and tissue damage. A range of organ systems may be involved simultaneously or sequentially. The manifestations of lupus include arthritis, pleuritis, pericarditis, stroke, seizure, nephritis, vasculitis, anemia, thrombocytopenia, alopecia, photosensitivity, and malar rash. Over time, patients with lupus accrue irreversible organ damage which contributes to an increased mortality rate in these patients. Despite advances over the past 40 years in both diagnosis and treatment, patients with SLE have a 2 - 5-fold greater risk of mortality.

SLE most often develops between the ages of 15 – 44 with an insidious onset (Danchenko et al, 2006). In the US, the estimated average of the reported prevalence is approximately 10 cases per 10,000 persons, representing about 300,000 patients, and the incidence has increased 2.5-fold between 1950 and 1979 (Uramoto et al, 1999; Somers et al, 2007; Balluz et al, 2001; Naleway et al, 2005; Ward, 2004; Helmick et al, 2008). In the European Union, an estimated overall average of the reported prevalence is 4 to 5 cases per 10,000 persons (Alamanos et al, 2003; Benucci et al, 2005; Eilertsen et al, 2006; Gourley et al, 1997; Govoni et al, 2006; Gudmundson et al, 1990; Hopkinson et al, 1993; Johnson et al, 1995; Lopez et al, 2003; Nightingale et al, 2007; Nossent, 2001; Piette et al, 2004; Samanta et al, 1992; Stahl-Hallengren et al, 2000; Voss et al, 1998). Recent studies by Bernatsky et al, have emphasized the increased risk of mortality in SLE and have provided data comparing all cause and disease-specific relative mortality across groups characterized by age, sex, SLE duration, calendar-year period, geographic location, and race (Bernatsky et al, 2006). A 2.4-fold greater risk of mortality (95% CI 2.3–2.5) was identified in SLE compared with the general population and there was an increased risk of death due to cardiovascular causes, malignancy, infections, and renal disease.

In an attempt to answer the question as to whether patients with SLE have an increased risk of malignancy in comparison to the general population, several large studies have recently been conducted. In a Swedish cohort of patients with SLE, Bjornadal et al (2002) used hospital discharge data to demonstrate an increased relative risk of any malignancy in SLE patients that was 25% higher than the general population. Of note, this finding was driven primarily by the higher incidence of non-Hodgkin's lymphoma (NHL) in the SLE population which had a relative risk that was 2.86-fold higher (95% CI 1.96, 4.04) than that of the general population. These findings have been subsequently confirmed by the Systemic Lupus International Collaborating Clinics (SLICC) research group in a larger international multi-center cohort study. Using standardized incidence ratio (SIR) estimates, a small increase in all malignancies combined was observed (SIR, 1.15, 95% CI 1.05, 1.27) for SLE compared to that expected for the general population based on data from regional cancer registry linkages (Bernatsky et al, 2005). Similarly, the increased risk for NHL was also demonstrated (SIR, 3.64, 95% CI 2.63, 4.93) in the SLE

population compared with the general population. Unfortunately, no investigations have been able to establish the reason for the close association between SLE and malignancy. Potential considerations for this association include abnormal immune activity early in the course of the disease, as well as cumulative exposure to immunosuppressive medications. In the SLICC international multi-center cohort study, the adjusted hazard ratio (HR) for overall risk of malignancy after administration of any immunosuppressive drug was 0.82 (95% CI 0.50 1.36). However, when specifically considering hematological malignancies, there was a suggestion of an increased risk after immunosuppressive drug exposures particularly when the medication exposures were lagged by a period of 5 years (adjusted HR 2.29, 95% CI 1.02-5.15).

Infections are responsible for morbidity and mortality in 25-50% of SLE patients; they are an important cause of death in SLE patients in developing countries (Alarcón et al, 2001; Cervera et al, 1999; Graciela et al, 2006). In a multi-center European study in which 1,000 SLE patients were followed for more than 5 years, infections and disease activity were found to be responsible for more than half of all deaths. Moreover, patients with SLE have higher rates of infections and poorer outcomes compared to the general population (Doria et al, 2008; Petri, 1998). The microorganisms responsible for the overwhelming majority of infections in patients with SLE are bacteria with gram negative and gram positive being the most common. However, there are many reports of infections occurring in patients with SLE with various outcomes as a consequence of other microorganisms. The increased susceptibility to infections may be multifactorial. Disease activity has been shown to be an independent risk factor for the occurrence of infections (Petri et al, 1992; Zonana-Nacach et al, 2001) presumably because of the abnormal cellular function and complement abnormalities that are more pronounced in the affected patients. The use of corticosteroids and other immunosuppressive medications has also been associated with the increased occurrence of infections in SLE (Gladman et al, 2002; Noel et al, 2001; Petri et al, 1992). Consequently, the possibility exists that the increased occurrence of infections may be a consequence of cytokine suppression, resulting in multiple cellular functional abnormalities (Boumpas et al, 1993).

Neuropsychiatric events are well recognized in the SLE population, with a wide range of incidence. In an international inception cohort study (Hanly, 2007), neuropsychiatric events occurred in 28% of subjects near the time of SLE diagnosis, and the incidence of mood disorders attributed to SLE ranged from 4% to 13% depending on the attribution model used. Another study (Bachen et al, 2009) found the prevalence rates of many psychiatric disorders (major depressive disorder, bipolar disorder, panic disorder, etc.) were significantly higher in patients with SLE than the general population. The rate of major depression reported in the literature for patients with SLE ranges from 22.5%-39.1% (Nery et al, 2007; Brey et al, 2002; Ainiala et al, 2001). Severe depression requiring hospitalization was found to be 0.26% (14/5371 SLE patients in a Swedish cohort followed from 1973 to 2004) (Sundquist et al, 2008). Chronic physical illness is also an important risk factor for suicide (Karassa et al, 2003). Patients with SLE are at almost 5 times greater risk for suicide than expected (Harris et al, 1994). Suicide attempts among SLE patients was 5/300 SLE patients who visited a UK Rheumatology Clinic over a 20-year period (1979-1999) (Karassa et al, 2003) with deaths attributed to suicide ranging from 0.23-0.95% (Mok et al, 2008; Nossent, 2001; Karassa et al, 2003).

1.2 Study Agent Background Relevant to Clinical Study

Belimumab (BENLYSTA™) is a recombinant human IgG1λ monoclonal antibody that binds to soluble human B-lymphocyte stimulator (BLyS; also known as B cell activating factor belonging to the tumor necrosis factor (TNF) family [BAFF] and TNFSF13B) and inhibits its biological activity (Baker, 2003). GlaxoSmithKline (GSK) received its first approval of belimumab on 09 March 2011 in United States (US) for treatment of SLE at a dosage regimen of 10 mg/kg at 2-week intervals for the first 3 doses and at 4-week intervals thereafter. Belimumab is currently approved in the US, all EU Member States, as well as 40 further countries. These approvals were based on the data from two Phase 3 trials in 1,684 patients where belimumab 10 mg/kg plus standard therapy demonstrated superiority over placebo plus standard therapy in reduction in disease activity as measured by the SLE responder index (SRI) with an acceptable safety profile. Reduction in steroid use and risk of severe flare was also observed, but not consistently across trials. Reductions in anti-dsDNA antibodies and increases in complement levels were observed.

The current primary belimumab safety population, includes safety data from the double-blind portion of the Phase 2/3 studies submitted with the original IV marketing application, as well as double-blind studies of beliumumab administered subcutaneously (SC) in SLE subjects and IV in SLE subjects located in the North East region of Asia. A summary of adverse events of special interest, including deaths, in this dataset is provided below. Additional information is provided in the Investigator's Brochure.

Deaths from belimumab SLE studies are summarized in Table 1-1; this includes a 3 study pooled IV dataset (data presented in the original marketing authorization submissions), and more recent data generated from studies performed with IV belimumab in North East Asia (BEL113750) and from a study in which belimumab was administered SC (BEL112341). A total of 20 deaths have occurred in this primary safety population: 6/1190 (0.504%) received placebo, and 14/2484 (0.564%) received belimumab. No single cause of death has predominated and etiologies included infection, cardiovascular disease and suicide.

Table 1-1 Deaths in Belimumab IV and SC SLE Controlled Repeat Dose Studies

	C1056/C1057/LBSL02 Pooled IV		BEL112341 SC		BEL113750 IV	
	Pbo N=675	Bel N=1458	Pbo N=280	Bel N=556	Pbo N=235	Bel N=470
n n/N%	3 0.4%	11 0.8%	2 0.7%	3 0.5%	1 0.4%	0 0%

n=number of subjects

Likewise, rates of adverse events of special interest (AESIs), including malignancy, infection and psychiatric events are summarized in Table 1-2 for data generated in IV and SC controlled, repeat dose belimumab studies.

Table 1-2 AESIs in Belimumab IV and SC SLE Controlled Repeat Dose Studies

	C1056/C1057/LBSL02 Pooled IV		BEL112341 SC		BEL113750 IV	
	Pbo N=675	Bel N=1458	Pbo N=280	Bel N=556	Pbo N=235	Bel N=470
Malignancies including NMSC						
n	2	5	1	2	0	1
n/N%	0.3%	0.3%	0.4%	0.4%	0%	0.2%
Malignancies excluding NMSC						
n	1	2	1	2	0	1
n/N%	0.1%	0.1%	0.4%	0.4%	0%	0.2%
Serious Infections of Special Interest						
n	5	19	3	8	7	11
n/N%	0.7%	1.3%	1.1%	1.4%	3.0%	2.3%
Opportunistic Infections						
n	8	15	1	2	5	13
n/N%	1.2%	1.0%	0.4%	0.4%	2.1%	2.8%
Depression/Suicide/Self Injury						
n	56	146	10	17	6	10
n/N%	8.3%	10.0%	3.6%	3.1%	2.6%	2.1%

Malignancies (excluding NMSC) assessed across all IV and SC SLE belimumab studies as of 08 March 2016, including safety data from double-blind and open-label studies/portions of studies and adjusted for patient-years exposure were compared with the malignancy rate in SLE patients reported in a large international cohort study of cancer in SLE (Bernatsky et al, 2005). Excluding NMSC, the malignancy rate per 100 patient-years with belimumab is 0.45 (95% CI 0.33, 0.59) compared with a background rate in SLE patients of 0.53 (95% CI 0.48, 0.59). Excluding NMSC is appropriate given that they are generally nonserious events with a high cure rate and it is known that NMSC is underreported in observational studies compared with prospective clinical trials (Great Britain National Cancer Statistics, 2010; Young et al, 2007). No pattern of malignancies or increase in any particular type of malignancy was identified in patients receiving belimumab other than would be expected in an SLE population with a predominance of women.

In the randomized-controlled IV SLE trials, infections occurred slightly more often in belimumab groups compared with the placebo group; although, severe and serious events occurred at similar rates across the placebo and the belimumab groups. In the randomized-controlled SC SLE study, similar rates of infections, including severe and serious events, occurred in the belimumab 200 mg SC group and placebo group. The rate of opportunistic infections to date among belimumab study subjects and post-marketing approval patients appears less than the range reported in the literature for patients with SLE, 1.10 per 100 patient-years (95% CI: 0.67, 1.7) as compared to 2.50 per 100 patient years (95% CI: 1.21, 4.55) (Gladman, 2002; Zonana-Nacach, 2001).

Across all SLE studies of belimumab through 08 March 2016, the incidence rate of completed suicide for belimumab-treated subjects was 36 per 100,000 subject-years (95%

CI: 9.83, 92.38). The incidence rate of suicidal behavior (suicide attempt and completed suicide) was 180 per 100,000 subject-years (95% CI: 110.20, 278.62). The incidence rate of suicidal ideation was 108 per 100,000 subject-years (95% CI: 55.93, 189.08). These estimates are consistent with the background rates for completed suicide (10 to 2181 per 100,000 patient-years (Cervera, 2003; Li-Yu, 2007) and for suicide and suicide attempts (117 per 100,000 patient-years; 95% CI: 46.9, 240) reported for SLE patients in observational studies or retrospective chart reviews (Karassa, 2003). Furthermore, review of clinical trial, as well as postmarketing data, of suicide and suicidal thoughts and/or behavior did not identify a pattern or establish an association with belimumab. It is known that SLE is associated with increased incidence of depression and suicide/suicidal ideation than in the general population.

Across all SLE studies of belimumab through 08 March 2016, the proportion of subjects with serious hypersensitivity reactions or infusion/injection-related reactions was 31/5366 subjects (0.58%) or 0.28 per 100 subject-years (95% CI: 0.19, 0.40). The estimated incidence rate of serious hypersensitivity reactions or infusion/injection-related reactions in spontaneous and postmarketing reports was 0.32 per 100 patient-years (95% CI: 0.26, 0.38). The majority of serious hypersensitivity events have occurred on the 1st infusion, although there have been reports of hypersensitivity events occurring after several infusions of belimumab. Most clinical trial and spontaneous cases of serious hypersensitivity occurred during or within the first hour after the completion of the infusion. The majority of reports of infusion-related and hypersensitivity reactions were non-serious and included symptoms such as nausea, vomiting, diarrhea, chills, fever, rash, urticaria, pruritus, headache, dizziness, and dyspnoea. However, infusion and hypersensitivity reactions can be severe and fatal.

1.3 Rationale for the Study

The primary goal of lupus treatment is to control or halt the inflammatory disease process while minimizing the side effects and the risk of infection that are associated with current therapies. The treatments historically and currently used for SLE have broad effects on immune and inflammatory pathways. Standard therapies for SLE include corticosteroids, antimalarial agents, non-steroidal anti-inflammatory drugs, and immunosuppressive agents. The available therapies are similar in US, Europe and the rest of the world. In addition to the disease itself, these treatments also cause short- and long-term morbidity. Agents such as cyclophosphamide are both cytotoxic and immunosuppressive and can result in increased risk of premature ovarian failure, serious infection, and cancer. Long-term use of high-dose corticosteroids can cause cataracts, osteoporosis, avascular necrosis, metabolic disorders, increased infections, edema, weight gain, and hyperlipidemia. Belimumab is approved in numerous markets world wide and is a BLyS-specific inhibitor that blocks the binding of soluble BLyS, a B-cell survival factor, to its receptors on B cells. Belimumab does not bind B cells directly, but by binding BLyS, belimumab inhibits the survival of B cells, including autoreactive B cells, and reduces the differentiation of B cells into immunoglobulin-producing plasma cells.

In Phase 3 clinical trials belimumab was shown to be effective in the treatment of patients with active, autoantibody-positive SLE; patients with severe active lupus nephritis and

severe active central nervous system lupus were excluded from the studies, as were patients receiving intravenous cyclophosphamide and other biologics. Furthermore, belimumab was generally safe and well-tolerated, including with long term use in a subset of patients, albeit in an uncontrolled setting. While substantial information exists about the safety of belimumab from these clinical trials, the present study is intended to evaluate a larger number of subjects in a controlled setting. The safety objectives of the study are intended to focus on areas where a numerical imbalance in the frequency and rates were observed across treatment groups in the controlled trials included with the original marketing applications (i.e., mortality, selected psychiatric events/suicidality, serious infusion and hypersensitivity reactions) or where there is a theoretical basis for increased risk with an immunomodulatory treatment (ie, serious/opportunistic infections, malignancy).

The study design is considered optimal to address these safety objectives. The study is double-blind, placebo-controlled for 1 year. During this time, all safety endpoints as described in Section 8.5.1 will be evaluated. This study also affords the opportunity to evaluate steroid reduction at Weeks 40-52.

1.4 Benefit-Risk Assessment

1.4.1 Risk Assessment

Belimumab administered by IV infusion is indicated for reducing disease activity in adult patients with active autoantibody positive SLE who are receiving standard therapy. The benefit/risk profile of belimumab for SLE remains favorable.

Identified risks include hypersensitivity/infusion reactions and infections. Potential risks (i.e., based on pharmacology but no association identified to date) include progressive multifocal leukoencephalopathy (PML); malignancies; immunogenicity; effects on immunizations (including interactions with live vaccine); and psychiatric events including depression and suicidality.

The most common AEs reported in the primary safety population of adults with SLE were associated with hypersensitivity/infusion related reactions, infections, and symptoms consistent with SLE. The majority of reports of infusion-related and hypersensitivity reactions were non-serious and include symptoms such as nausea, vomiting, diarrhea, chills, fever, rash, urticaria, pruritus, headache, dizziness, and dyspnoea. However, infusion and hypersensitivity reactions can be severe and fatal. Most clinical trial and spontaneous cases of serious hypersensitivity occurred during or within the first hour after the completion of the infusion, although some cases report delayed acute onset (>4 hours but <4 days) or a delayed non-acute onset (4-21 days) hypersensitivity reactions.

Infections have been reported with administration of belimumab and are also associated with both SLE and immunosuppressant medication used to treat SLE. The mechanism of action of belimumab may increase the potential risk for the development of infections.

Table 1-3 provides a summary of key issues, their impact, and strategy to mitigate risk in this study.

Table 1-3 Summary of Key Issues, Their Impact and Strategy to Mitigate Risk

Identified Risks	Summary of Data	Impact – Eligibility Criteria	Strategy and Monitoring
Post-infusion systemic reactions and Hypersensitivity	Administration of IV belimumab may result in infusion and hypersensitivity reactions, which can be severe and can be fatal. Non-serious infusion reactions and hypersensitivity reactions are common in SLE clinical trials with IV belimumab. Serious infusion and hypersensitivity reactions affected less than 1% of patients and included anaphylactic reaction, bradycardia, hypotension, angioedema, and dyspnea. Delays in the onset of hypersensitivity reactions have been observed. Infusion reactions following administration of belimumab occurred more frequently on the first 2 infusion days and tended to decrease with subsequent administrations. Delayed-type, non-acute hypersensitivity reactions have also been observed and included symptoms such as rash, nausea, fatigue, myalgia, headache, and facial oedema.	This identified risk does not directly impact eligibility criteria.	Subjects should remain under clinical supervision for 3 hours after completion of the first 2 infusions. Should symptoms of acute hypersensitivity occur, an extended period of monitoring may be appropriate, based on clinical judgment. Otherwise, subjects will be monitored during and after each infusion according to study sites' guidelines or standard operating procedure for IV infusions. This may include, but is not limited to, monitoring vital signs and observing for any untoward reactions. Subjects should be made aware of the potential risk, the signs and symptoms of such reactions, and the importance of immediately seeking medical attention. Belimumab should be administered by a healthcare professional prepared to treat hypersensitivity reactions including anaphylaxis.
Infections	Infections occurred in a slightly greater proportion of subjects treated with IV belimumab compared with placebo. Infections occurring in at least 3% of patients receiving belimumab and at least	Exclude patients with any of the following: currently on any suppressive therapy for a chronic infection; hospitalization for treatment of an infection within 60	Subjects should be made aware of the potential risk, the signs and symptoms of infection, and the importance of immediately seeking medical attention. Infections should be identified and treated appropriately.

Identified Risks	Summary of Data	Impact – Eligibility Criteria	Strategy and Monitoring
	1% more frequently than patients receiving placebo were nasopharyngitis, bronchitis, pharyngitis, cystitis, and gastroenteritis viral. Serious infections, occurred in 5% of patients receiving either belimumab or placebo.	days of Day 0; use of IV or IM antibiotics within 60 days of Day 0; a history of or positive test at screening for HIV, hepatitis B or hepatitis C;	

Potential Risks	Summary of Data	Impact – Eligibility Criteria	Strategy and Monitoring
Progressive multifocal leukoencephalopathy (PML)	No association between belimumab and the risk of opportunistic infections, including PML, has been indentified to date, but data are limited. PML resulting in neurological deficits, including fatal cases, has been reported in SLE patients receiving immunosuppressant pharmacotherapy, including belimumab.	This potential risk does not directly impact eligibility criteria.	Subjects should be made aware of this potential risk, the signs and symptoms of PML, and the importance of immediately seeking medical attention. A diagnosis of PML should be considered in any subject presenting with new-onset or deteriorating neurological signs and symptoms. The subject should be referred to a neurologist or other appropriate specialist for evaluation. If PML is confirmed, study agent should be discontinued and consideration should be given to stopping immunosuppressant therapy. If PML is suspected, this should be immediately reported to the Medical Monitor. The appropriateness of continuing study agent, while the case is being assessed, should be discussed.
Malignancies	As with other immunomodulating agents, the mechanism of action of belimumab	Exclude patients with a history of malignant neoplasm within the	Monitor patients for signs and symptoms of malignancy. Subjects should be made aware

Potential Risks	Summary of Data	Impact – Eligibility Criteria	Strategy and Monitoring
	may increase the potential risk for the development of malignancies.	last 5 years, except for adequately treated basal or squamous cell cancers of the skin, or carcinoma in situ of the uterine cervix.	of the potential risk, and the importance of immediately seeking medical attention with any related signs or symptoms.
Immunogenicity	As with other monoclonal antibodies, treatment with belimumab could lead to the development of anti-drug antibodies (ADA). Among SLE subjects treated with belimumab, the proportion of subjects who developed persistently positive ADA was low and very few of the persistently positive antibodies were found to be neutralizing. Neither development of ADA nor persistent ADA was associated with infusion or hypersensitivity reactions. As expected, the proportions of subjects with persistent ADA increased slightly over time in belimumab-treated subjects but there was no increase in the number of subjects with neutralizing antibodies or the number reporting infusion-related adverse events.	This potential risk does not directly impact eligibility criteria.	Monitor adverse events.
Effects on immunizations including reactions with live vaccines	No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving belimumab. Because of its mechanism of action, belimumab may interfere with the response to immunisations.	Exclude patients who have received a live vaccine within 30 days of Day 0.	Live vaccines are prohibited during the study conduct. Subjects should be made aware of the potential risk for impact of belimumab on vaccine response.

Potential Risks	Summary of Data	Impact – Eligibility Criteria	Strategy and Monitoring
	However, in a study evaluating the response to a 23-valent pneumococcal vaccine, overall immune responses to the different serotypes were similar in SLE patients receiving belimumab compared with those not receiving treatment at the time of vaccination. Limited data suggest that belimumab does not significantly affect the ability to maintain a protective immune response to immunisations received prior to administration of belimumab.		
Potential psychiatric events - Depression and suicidality	There have been reports of depression and suicidality in patients receiving belimumab. The estimated rates of suicidality for belimumab remain consistent with the rates of the background SLE population. The background rate for completed suicide identified in the literature ranged from 0.01 to 2.17 per 100 PY and varied by study type (clinical trial or observational study) [Li-Yu 2007; Cervera 2003]. The background rate for suicidal behavior (completed suicide and attempts) is 0.12 (95% CI 0.05, 0.24)/100 patient years [Karassa 2003].	This potential risk does not directly impact eligibility criteria.	Perform suicidality assessment by using the Columbia Suicidality-Severity Rating Scale (C-SSRS) Screening form at baseline and every visit, and monitor results. Subjects should be made aware of the potential risk and should report signs and symptoms.

Refer to Section 8.3 for information about the Independent Data Monitoring Committee (IDMC) being used in the study.

1.4.2 Benefit Assessment

The primary data supporting efficacy and the approval of IV belimumab were the Phase 3 trials (C1056 and C1057) in which 1,684 subjects were treated for up to 52 weeks (C1057) or 76 weeks (C1056) (Belimumab IB, Section 5.3.1.2). Belimumab produced significant improvements in the SLE Responder Index as well as in individual component SELENA-SLEDAI score in both studies. Pooled analyses demonstrated steroid sparing, delay in median time to first flare, and decreased risk of severe flares over 52 weeks. Clinical trial data for belimumab since approval continue to show efficacy in the treatment of SLE through decreased SLE flares and decreased disease activity across multiple organ systems (Belimumab IB, Section 5.3.1.3).

1.4.3 Overall Benefit:Risk Conclusion

The safety profile of belimumab remains consistent with that known at approval and is consistent with expected events based on the mechanism of action and the disease under study. Appropriate risk mitigation measures are in place; rare and long-term risks will be further evaluated via the large safety study and registry, ongoing and future studies, and routine pharmacovigilance. Review of safety data is conducted on a continual basis in order to identify new safety signals which may arise from clinical trial and/or post-marketing reports. The benefit: risk profile of belimumab for SLE continues to be favorable.

2 Study Objectives

The objectives of this study are to evaluate the following in adult SLE subjects receiving belimumab plus standard therapy versus subjects receiving placebo plus standard therapy:

- Mortality and adverse events of special interest over 1 year (through 52 weeks).
- Corticosteroid reduction during Weeks 40-52.

3 Study Design

3.1 Basic Design Characteristics

This is a global, multi-center, randomized, placebo-controlled study to evaluate adverse events of special interest in adults with active, autoantibody-positive systemic lupus erythematosus (SLE) treated with belimumab plus standard therapy vs placebo plus standard therapy. Originally, approximately 5,000 subjects were planned to be randomized to 1 of 2 treatment groups: belimumab 10 mg/kg (2,500 subjects) or placebo (2,500 subjects) plus standard therapies. Subsequent to the reporting of additional placebo controlled data, the sample size was reduced to 4,000 subjects in total.

Subjects will receive study agent (belimumab or placebo) on Days 0, 14, 28 and approximately every 28 days thereafter through Week 48 with a final visit conducted at Week 52. Subjects who discontinue treatment at any time during the 52-week study will be followed for mortality and malignancy (including NMSC) at 1 year (through Week 52) and annually for Years 2 through 5.

Subject data will be collected at randomization and subsequently at approximately 28-day intervals for 52 weeks. Subjects will be assessed for malignancies, including NMSC, serious infections, opportunistic infections and other infections of interest, selected serious psychiatric events, suicidality, and serious infusion and hypersensitivity reactions. All cause mortality will be reported. All other serious adverse events (SAEs), irrespective of causality, will also be recorded. Medical history will be collected on all subjects. Immunomodulatory agents used to treat SLE at baseline and during study, hospitalizations, and organ damage (SLICC/ACR Damage Index) will also be assessed through Week 52.

All subjects will have a follow-up visit performed approximately 4 weeks after the last dose of study agent. In the event that a subject withdraws consent to participate in the first year monthly study visits, an attempt should be made at the time of consent withdrawal to obtain consent to contact the subject at Week 52 and annually for Years 2 through 5 (Week 260) to assess mortality and malignancy (including NMSC).

Subjects may continue to receive their other SLE medications including corticosteroids, immunomodulatory agents, and antimalarials. Changes in these SLE medications during the trial will be permitted as clinically indicated. No concomitant biological therapies will be allowed during the 52-week study. In the event that the treating physician decides that a subject requires the addition of a biologic agent before Week 52, the subject is withdrawn from study agent but is followed on study through Week 52 and annually for Years 2 through 5 (Week 260).

Following the 52-week study, all subjects will be contacted annually through Year 5 (Week 260) to assess mortality and malignancy (including NMSC).

At the end of the 52-week study, subjects who wish to continue treatment may be able to do so by being prescribed commercially available belimumab. If belimumab is not commercially available in a subject's country of participation, the subject may be able to receive belimumab under a separate continuation protocol. A separate informed consent will need to be provided for the continuation protocol.

An Independent Data Monitoring Committee (IDMC) will review unblinded safety data for this study on an ongoing basis until the data are locked and analyzed. The IDMC will include at least 3 physicians, and a statistician, none of whom are affiliated with the sponsor. The first IDMC meeting will review the data after approximately 500 subjects are enrolled or 6 months from randomization of the first patient, whichever is first. After the initial review, the IDMC will continue to review data approximately every 6 months. Events to be monitored during the

safety review will include at a minimum all serious adverse events (including deaths, serious psychiatric events and serious infections), opportunistic infections (serious and nonserious) and other infections of interest, malignancies (including NMSC), and serious infusion and hypersensitivity reactions. Investigators and IRBs/IECs will be notified of the outcome of each IDMC meeting.

4 Inclusion and Exclusion Criteria

4.1 Inclusion Criteria

Subjects enrolled in the study must meet the following inclusion criteria:

1. Males or females ≥ 18 years.
2. Have a diagnosis of SLE, refer to ACR revised criteria for the classification of SLE (Appendix 1) as a guide for diagnosis of SLE.
3. Active, autoantibody positive SLE (autoantibody positive is defined as the presence of ANA or anti-dsDNA antibodies).
4. Are on a SLE treatment regimen consisting of any of the following medications (alone or in combination):
   - Corticosteroids
   - Other immunomodulatory agents including methotrexate, azathioprine, leflunomide, mycophenolate (including mycophenolate mofetil, mycophenolate mofetil hydrochloride, and mycophenolate sodium), calcineurin inhibitors (eg, tacrolimus, cyclosporine), sirolimus, oral cyclophosphamide, 6-mercaptopurine, or thalidomide.
   - Anti-malarials [eg, hydroxychloroquine, chloroquine, quinacrine (mepacrine)].
5. A female subject is eligible to enter the study if she is:
   - Not pregnant or nursing;
   - Of non-childbearing potential defined as:
     - pre-menopausal females with a documented tubal ligation, hysterectomy, documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion, or documented bilateral oophorectomy or
     - post-menopausal defined as 12 months of spontaneous amenorrhea with an appropriate clinical profile [e.g., > 45 years, in the absence of hormone replacement therapy or other cause for amenorrhea]; in questionable cases obtain a blood sample for follicle stimulating hormone (FSH) and estradiol simultaneously to confirm. Diagnostic levels for FSH and estradiol vary by specific laboratories/assays;
   - OR is of child-bearing potential with negative pregnancy test as determined by urine human chorionic gonadotrophin (hCG) test at screening and urine hCG test prior to dosing AND
     - Agrees to use one of the contraception methods listed in the protocol (see Section 4.3) for 2 weeks prior to the day of dosing to sufficiently minimize the risk

of pregnancy at that point. Female subjects must agree to use contraception until 16 weeks following the last dose of study agent.

- OR has only same-sex partners, when this is her preferred and usual lifestyle.

6. Have the ability to understand the requirements of the study, provide written informed consent (including consent for the use and disclosure of research-related health information), and comply with the study data collection procedures [including annual contacts from Years 2 through 5 (Week 260) to assess mortality and malignancy].

4.2 Exclusion Criteria

Subjects will be excluded from participating in the study if they meet any of the following exclusion criteria:

1. Have received any prior treatment with belimumab, either as a marketed product or as an investigational agent.
2. Have received treatment with B cell targeted therapy (eg, rituximab, other anti-CD20 agents, anti-CD22 [epratuzumab], anti-CD52 [alemtuzumab], BLyS-receptor fusion protein [BR3], TACI-Fc, anti-BAFF [LY2127399]) within 364 days of Day 0.
3. Have received any of the following within 90 days of Day 0:
   - Any biologic agent (eg, adalimumab, etanercept, infliximab, anakinra) other than B cell targeted therapy (see Exclusion Criterion 2).
   - Plasmapheresis.
4. Have received any of the following within 60 days of Day 0:
   - A non-biologic investigational agent.
5. Have received any of the following within 30 days of Day 0:
   - A live vaccine.
6. Have a history of malignant neoplasm within the last 5 years, except for adequately treated cancers of the skin (basal or squamous cell) or carcinoma in situ of the uterine cervix.
7. Have required management of acute or chronic infections, as follows:
   - Currently on any suppressive therapy for a chronic infection (such as tuberculosis, pneumocystis, cytomegalovirus, herpes simplex virus, herpes zoster and atypical mycobacteria).
   - Hospitalization for treatment of infection within 60 days of Day 0.
   - Use of parenteral (IV or IM) antibiotics (antibacterials, antivirals, anti-fungals, or anti-parasitic agents) within 60 days of Day 0.
8. Have severe lupus kidney disease (defined by proteinuria > 6 g/24 hour or equivalent using spot urine protein to creatinine ratio, or serum creatinine > 2.5 mg/dL), or have severe active nephritis requiring acute therapy, or have required hemodialysis or high-dose prednisone or equivalent (> 100 mg/day) within 90 days of Day 0.

9. Have severe active central nervous system (CNS) lupus (including seizures, psychosis, organic brain syndrome, cerebrovascular accident [CVA], cerebritis or CNS vasculitis) requiring therapeutic intervention.
10. Known HIV infection.
11. Current or history of hepatitis B or hepatitis C infection.
12. ***Only applicable to Lithuanian sites:***
    - Have hypogammaglobulinaemia (IgG <400 mg/dL) or a deficiency in immunoglobulin A (IgA <10 mg/dL).
    - Have had renal, stem cell/marrow or other major organ transplant.
    - Have a chronic infection or a history of recurrent infections, which in the opinion of the investigator poses a significant risk to the subject.
    - Have received cyclophosphamide via any route of administration within 90 days of Day 0.

4.3 Contraception Requirements for Female Subjects

Female subjects of childbearing potential must not become pregnant during the study and so must be sexually inactive by abstinence or use contraceptive methods with a failure rate of < 1%. Female subjects of childbearing potential with same sex partners (when this is their preferred and usual lifestyle) are not required to be abstinent or to use contraception.

Abstinence

Sexual inactivity by abstinence must be consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Contraceptive Methods with a Failure Rate of < 1%

- Oral contraceptive, either combined or progestogen alone
- Injectable progestogen
- Implants of levonorgestrel or etonogestrel
- Estrogenic vaginal ring
- Percutaneous contraceptive patches
- Intrauterine device (IUD) or intrauterine system (IUS) with <1% failure rate as stated in the product label
- Male partner sterilization (vasectomy with documentation of azoospermia) prior to the female subject's entry into the study, and this male is the sole partner for that subject. For this definition, “documented” refers to the outcome of the investigator's/designee’s review of the subject's medical history for study eligibility, as obtained via a verbal interview with the subject or from the subject’s medical records.

- Double barrier method: condom and occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent (foam/gel/film/cream/suppository).

NOTE: MMF and other forms of mycophenolate affect the metabolism of oral contraceptives and may reduce their effectiveness. As such, women receiving mycophenolate who are using oral contraceptives for birth control should employ an additional method (e.g., barrier method).

NOTE: These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

5 Study Treatment Regimen

5.1 Study Agent Name and Formulation

The common name of the investigational product is BENLYSTA™. The generic (USAN/INN) name is belimumab.

Belimumab is a recombinant human, IgG1λ monoclonal antibody specific for soluble human B lymphocyte stimulator (BLyS, also referred to as BAFF and TNFSF13B). Belimumab has a molecular weight of approximately 147 kDa. Belimumab is produced by recombinant DNA technology in a mammalian cell expression system.

Belimumab study agent is provided as a sterile, lyophilized product. Upon reconstitution with 4.8 mL sterile water for injection (SWFI), each vial delivers 400 mg belimumab at 80 mg/mL in 0.16 mg/mL citric acid, 2.7 mg/mL sodium citrate, 80 mg/mL sucrose, 0.4 mg/mL polysorbate 80, pH 6.5. Each lyophilized vial is single use.

The placebo control is prepared as a sterile and lypholized product. Upon reconstitution with 4.8 mL SWFI, each vial will contain 0.16 mg/mL citric acid, 2.7 mg/mL sodium citrate, 80 mg/mL sucrose, 0.4 mg/mL polysorbate 80, pH 6.5. Each lyophilized vial is single use.

5.2 Packaging, Labeling, Preparation, and Storage

Belimumab will be supplied in a 20 mL vial containing 400 mg belimumab (deliverable).

Placebo control will be supplied in a 20 mL vial.

Lyophilized belimumab and placebo should be stored at 2-8°C. After reconstitution and dilution in normal saline, the material is stable for up to 8 hours at 2-8°C, or at room temperature. Refer to the Pharmacy Manual for detailed instructions on the preparation, administration, and storage of study agent.

The 400 mg single use vial of study agent will be reconstituted with 4.8 mL SWFI, to yield a final concentration of 80 mg/mL of belimumab. Placebo will be reconstituted with 4.8 mL SWFI.

In addition to any country-specific requirements, the study agent label will contain, at a minimum, the following information:

- Product name
- Concentration
- Lot number
- Storage conditions
- Investigational drug statement
- Sponsor's name and address

The calculated dose of study agent to be administered to the subject is determined in milligrams (mg) using the subject's current body weight in kilograms (kg) obtained at each visit prior to dosing. At sites where it is impractical to use the subject's current body weight to calculate the dose, it is permissible for the Week 2 visit onward to use the subject's body weight from the previous visit (e.g., the Day 0 weight can be used to calculate the dose for the Week 2 visit). The current visit body weight must still be measured prior to dosing and if the current weight varies by more than 10% from the previous visit weight, then the weight measured at the current visit must be used to calculate the dose.

The reconstituted study agent will be diluted in 250 mL normal saline for IV infusion. An amount of normal saline, equal to the calculated amount of product to be added, should be removed from the infusion bag prior to adding the product. After adding the reconstituted product, gently invert the bag to mix the solution.

Belimumab and placebo will be supplied as open-label vials and 3rd party unblinding will be employed. The study agent will be reconstituted and diluted by the unblinded site pharmacist or designee, independent of the study (person responsible for receiving and dispensing study agent). Except for a limited number of safety oversight personnel, all other site personnel, the subject, the sponsor and contract research organization (CRO) will remain blinded to the study agent received. Separate monitors will be responsible for the clinical (blinded monitor) and study agent (unblinded monitor) aspects of the study.

Study agent inventory/accountability forms will be examined and reconciled by the unblinded monitor or designee as long as the study is blinded. After the end of the study all used and unused study agent must be accounted for on a study agent accountability form provided to the investigator by the sponsor, or its designee.

Refer to the Pharmacy Manual for more details regarding preparation, storage, handling, and drug accountability.

5.3 Dose, Route of Administration, and Schedule

There are 2 treatment groups: 10 mg/kg belimumab and placebo. Both treatment groups will receive other standard therapies, including steroids, immunomodulatory agents and antimalarials, as appropriate.

Once randomized, subjects will be dosed with study agent on Days 0, 14, 28 and then approximately every 28 days through Week 48.

Study agent should be administered by healthcare providers prepared to manage anaphylaxis. Prior to dosing with study agent, administration of premedication for prophylaxis against infusion reactions and hypersensitivity reactions may be considered. In the Phase 3 trials, 13% of subjects received premedication, which may have mitigated or masked a hypersensitivity response; however, there is insufficient evidence to determine whether premedication diminishes the frequency or severity of hypersensitivity reactions. All study agent treatments will be administered intravenously (IV) over no less than 1 hour. The rate of infusion may be slowed or interrupted if the subject develops an infusion reaction. In the event of a serious hypersensitivity reaction, administration of study agent must be discontinued immediately and appropriate medical therapy administered.

In the post-marketing setting, delayed onset of symptoms of acute hypersensitivity reactions has been observed. Subjects should remain under clinical supervision for 3 hours after completion of the first 2 infusions. Should symptoms of acute hypersensitivity occur, an extended period of monitoring may be appropriate, based on clinical judgment. This may include, but is not limited to, monitoring vital signs and observing for any untoward reactions. In addition, delayed-type, non-acute hypersensitivity reaction have also been observed and included symptoms such as rash, nausea, fatigue, myalgia, headache, and facial edema. Beyond the first 2 infusions, subjects should be monitored during and for an appropriate period of time after infusion according to study sites' guidelines or standard operating procedure for IV infusions.

Subjects should be made aware of the potential risk, the signs and symptoms of such reactions, and the importance of immediately seeking medical attention. For further information, see the belimumab Investigator's Brochure.

5.4 Alteration of Dose/Schedule Due to Toxicity

The dose of study agent administered may not be altered. The rate of infusion may be slowed or interrupted if the subject appears to develop signs of adverse reaction or infusion-associated symptoms. At later visits, these subjects may continue to be infused over a longer infusion period at the investigator's clinical discretion.

5.5 Concurrent Medications

5.5.1 Prohibited Medications

Subjects who require any prohibited medications during the 52-week study will have study agent discontinued, they will, however, remain on study and continue to be assessed according to the schedule outlined in the Study Calendar (Table 6-1). The following medications are prohibited during the study:

- Other investigational agents (biologic or non-biologic). Investigational applies to any drug not approved for sale in the country it is being used.
- Anti-TNF therapy (eg, adalimumab, etanercept, infliximab)
- Other biologicals (eg, commercial belimumab, rituximab, abatacept, interleukin-1 receptor antagonist [anakinra])
- Live vaccines

5.5.2 Allowable Medications

Subjects are enrolled on their current standard therapy for SLE. The medications used to treat SLE will be recorded at each visit during the study. These data will include the dose and frequency of corticosteroids as well as immunomodulatory and antimalarial agents.

6 Study Procedures

The nature of this study and the potential risks and benefits associated with participation in the study will be explained to all potential study subjects. Written informed consent must be obtained before the subject can begin any screening procedures that are not considered part of standard patient care.

Subjects participating in the pharmacogenetics (PGx) research portion of the protocol (see Section 9 and Appendix 7) must sign the PGx informed consent prior to any PGx samples being drawn from the subject.

Refer to the Study Calendar (Table 6-1) and the Study Procedures Manual.

6.1 Screening Procedures (Day -30 to Day 0)

The following should be performed within 30 days of the first dose of study agent (Day 0) as outlined in the Study Calendar (Table 6-1):

- Record demographics.
- Obtain medical history.
- Obtain history of and current SLE medications.
- Confirm diagnosis of SLE disease based on ACR criteria (Appendix 1) by reviewing previously documented clinical records.

- Perform suicidality assessment by using the Columbia Suicidality-Severity Rating Scale (C-SSRS) "Baseline/Screening" form (see Section 7.4 and Appendix 4).
- Complete SELENA SLEDAI (see Appendix 6).

  Note: To complete the SELENA SLEDAI, the following laboratory tests must be performed within 30 days prior to the SELENA SLEDAI assessment (within 60 days prior to randomization at Day 0): Hematology (WBC, platelets), complement (C3, C4), anti-dsDNA, routine urinalysis, and spot urine for macroscopic/microscopic/proteinuria assessments. [A dipstick for urine protein is NOT sufficient, measurement of 24 hr urine protein or a protein/creatinine ratio on a spot urine collection MUST be completed.]
- Pregnancy test (urine).
- Confirm subject meets study entry criteria.
- Subjects can be rescreened, if deemed appropriate by the Principal Investigator, but only once.

6.2 Study Enrollment Procedures

Subjects who have undergone all screening procedures and have met the entry criteria will be enrolled into the study and assigned to treatment by a central Interactive Web Response System (IWRS). Subjects will be randomized in a 1:1 ratio and stratified by region (US/Canada vs Central America/South America/Mexico vs Europe/Australia/Israel vs Asia), their screening SELENA SLEDAI score (≤ 9 vs ≥ 10), and steroid dose (≤ 7.5 mg/day or > 7.5 mg/day prednisone or equivalent).

6.3 Treatment Period

Subjects will be evaluated at the study site for the scheduled study visits outlined in the Study Calendar (Table 6-1). On Day 0, the subject will be randomized and receive the first dose of study agent. Subjects will be dosed at Week 2, Week 4 and approximately every 28 days (calculated from the Day 0 dose) thereafter through Week 48. The final treatment period evaluation for the study will occur at Week 52. Time windows are defined as ± 3 days for visits at Week 2 and Week 4, and ± 7 days for visits from Week 8 though Week 52. All study visits should occur within the visit window of the scheduled study visit. In rare circumstances, when the scheduled visit cannot be done within the visit window the Medical Monitor may be contacted for advice. Similarly, while all assessments for a dosing visit should be performed same day, in rare circumstances, an investigator may be permitted to conduct the assessments over two consecutive days so long as the infusion of the study agent is performed on the second day and after all other assessments.

All subjects who do not withdraw consent to participate in the first year monthly study visits and regardless of whether they continue to receive study agent will be followed on-study through Week 52 and annually for Years 2 through 5 (Week 260). All subjects will have a follow-up visit performed approximately 4 weeks after the last dose of study agent. In the

event that a subject withdraws consent to participate in the first year monthly study visits, an attempt should be made at the time of consent withdrawal to obtain consent to contact the subject at Week 52 and annually for Years 2 through 5 (Week 260) to assess mortality and malignancy (including NMSC).

6.4 Post-Treatment Follow-Up

All subjects will be contacted annually through Year 5 (Week 260) to assess mortality and malignancy (including NMSC) as outlined in the Study Calendar (Table 6-1). Annual follow-up also applies to subjects who discontinued study agent before Week 48. Time windows are ± 30 days for annual follow-up contacts from Year 2 to Year 5.

6.5 Discontinuation of Study Agent

Subjects will be free to discontinue study agent treatment at any time, for any reason, or the investigator may discontinue study agent treatment, if necessary, to protect the subject's health (see reasons for study agent discontinuation below). Subjects who discontinue study agent after receiving at least 1 dose of study agent will not be replaced. Subjects who discontinue study agent will continue to be followed on-study through Week 52 (regardless of changes in background medications) and annually for Years 2 through 5 (Week 260) according to the schedules outlined in Table 6-1. All subjects will have a follow-up visit performed approximately 4 weeks after the last dose of study agent (i.e., the follow-up visit is Week 52 for a subject who completes all dosing visits, and the follow-up visit is the next scheduled visit for a subject who discontinues study agent).

Subjects may have study agent discontinued for any of the following reasons:

- At the investigator's discretion.
- Requires:
  - Other investigational agents.
  - Anti-TNF therapy (eg, adalimumab, etanercept, infliximab).
  - Other biologicals (eg, commercial belimumab, rituximab, abatacept, interleukin-1 receptor antagonist [anakinra]).
  - Live vaccines.
- Lost to follow-up.

6.6 Withdrawal from Study

Subjects will be free to withdraw from the study at any time, for any reason. It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of subjects from study should be avoided.

If a subject withdraws consent to participate in the first year monthly study visits, at the time of consent withdrawal it is requested that the site attempt to obtain consent to contact the

subject at Week 52 and annually for Years 2 through 5 (Week 260) to assess mortality and malignancy (including NMSC).

Table 6-1 Study Calendar

Study Week	Screening visit (within 30 days of Day 0)	Day 0 visit	Wk 2 visit (Day 14 ± 3 d)	Wk 4 visit (Day 28 ± 3 d)	Wk 8 visit (Day 56 ± 7 d)	Wk 12 visit (Day 84 ± 7 d)	Wk 16 visit (Day 112 ± 7 d)	Wk 20 visit (Day 140 ± 7 d)	Wk 24 visit (Day 168 ± 7 d)	Wk 28 visit (Day 196 ± 7 d)	Wk 32 visit (Day 224 ± 7 d)	Wk 36 visit (Day 252 ± 7 d)	Wk 40 visit (Day 280 ± 7 d)	Wk 44 visit (Day 308 ± 7 d)	Wk 48 visit (Day 336 ± 7 d)	Wk 52 visit (Day 364 ± 7 d)	Annual Follow-up Years 2-5[11]
Written Informed Consent, Demographics, Medical History, SLE History/Diagnosis, Eligibility Criteria	x																
SELENA SLEDAI (related laboratory tests within 30 days prior to screening date)	x																
Pregnancy test[1]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Weight[2]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Baseline/screening suicidality assessment (C-SSRS **Appendix 4**)	x																
Since last visit suicidality assessment (C-SSRS **Appendix 5**)[3]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Study Agent Administration[4]		x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Record Concurrent Medications used to treat SLE	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Assess/Record Serious Adverse Events[5]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Assess/Record all Opportunistic Infections and Other Infections of Interest (including TB reactivation)[6]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Assess/Record all Malignancies (including NMSC)		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Assess/Record Serious Infusion and Hypersensitivity Reactions		x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Record Hospitalizations[7]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Pharmacogenetic Sampling (consenting subjects only)[8]		x															
SLICC/ACR Damage Index[9]		x														X[9]	
Survival Assessment[10]																x	x

Footnotes for the study calendar appear on the following page.

[1] A urine pregnancy test is required for women of child bearing potential. The results of urine pregnancy test must be available prior to dosing.
[2] The weight at the current visit should be used to calculate dose. Refer to Section 5.2 for further information.
[3] Suicidality is to be assessed prior to study agent infusion using the "Since Last Visit" C-SSRS (Appendix 5).
[4] Subjects should remain under clinical supervision for 3 hours after completion of the first 2 study agent infusions. Should symptoms of acute hypersensitivity occur, an extended period of monitoring may be appropriate, based on clinical judgment.
[5] All SAEs will be recorded. These data will be used to analyze serious infections and selected serious psychiatric events.
[6] Guidelines for opportunistic infections and other infections of interest are provided in Appendix 2.
[7] A hospitalization is an inpatient admission for any length of time. An admission for administration of study agent, for routine or planned clinical procedures, or for "social" reasons (not the result of any adverse change in the subject's condition) should not be recorded as a hospitalization.
[8] Pharmacogenetic sampling informed consent must be obtained prior to any blood being taken for PGx research. Sample should be drawn prior to dosing on Day 0. However, the sample may be collected at any time during the study.
[9] Refer to Appendix 3. SLICC/ACR Damage Index is only performed at Screening and Week 52 (but not earlier if a subject discontinues study agent).
[10] If asubject withdraws consent to participate in the first year monthly study visits, it is requested that the site attempt to obtain consent to contact the subject at Week 52 and annually for Years 2 through 5 (Week 260) to assess mortality and malignancy (including NMSC)..
[11] Following the study, all subjects will be contacted annually through Year 5 (Week 260) to assess mortality and malignancy (including NMSC).

6.7 Subject Unblinding

Belimumab and placebo will be supplied as open-label vials and 3rd party unblinding will be employed. The study agent will be reconstituted and diluted by the unblinded site pharmacist or designee, independent of the study (person responsible for receiving and dispensing study agent). Except for a limited number of safety oversight personnel, all study site personnel, the subject, the sponsor and the Contract Research Organization (CRO) remain blinded to the study agent received. Separate monitors will be responsible for the clinical (blinded monitor) and study agent (unblinded monitor) aspects of the study.

In the case of a medical emergency when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject, the study blind may be broken for the specific subject. Whenever possible, the investigator should discuss options with the Medical Monitor prior to unblinding any subject. If this is impractical, the investigator must notify the Medical Monitor as soon as possible of any broken blind, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study. Any broken blind will be clearly justified and explained by a comment in the eCRF.

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to clinical investigators in accordance with local regulations and/or GSK policy.

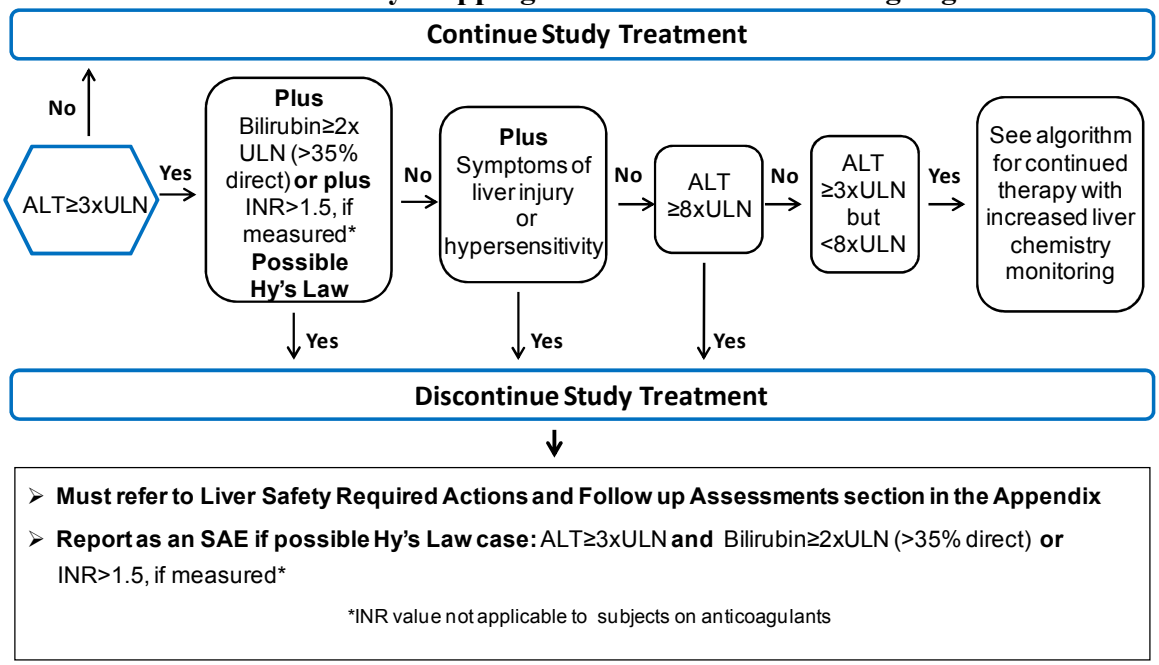
6.8 Laboratory Tests (Liver Stopping Criteria)

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

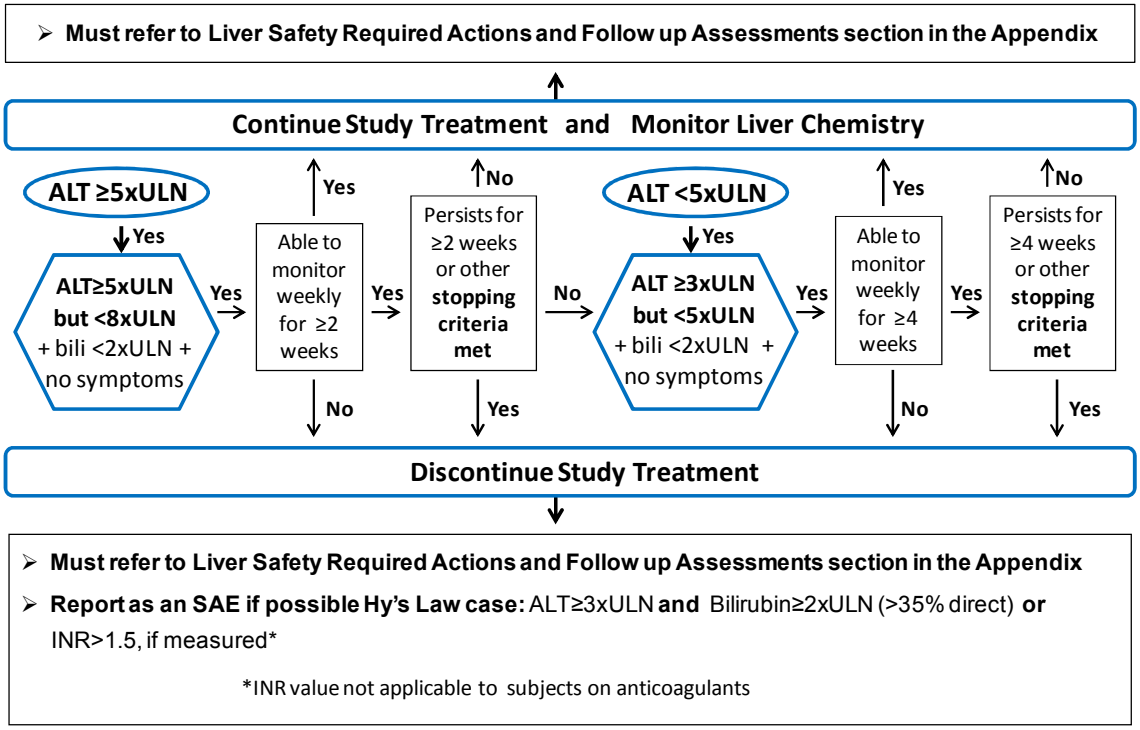
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Although routine safety laboratory is not required per protocol, in the event the investigator becomes aware that liver function test (LFT) monitoring was performed, the LFT results should be evaluated against the liver stopping criteria and the GSK Medical Monitor must be contacted.

Phase III-IV Liver Chemistry Stopping and Increased Monitoring Algorithm



Phase III-IV Liver Chemistry Increased Monitoring Algorithm with Continued Therapy for ALT ≥3xULN but <8xULN



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 9.

6.8.1 Study Agent Restart or Rechallenge

If subject meets liver chemistry stopping criteria do not restart/rechallenge subject with study treatment unless:

- GSK Medical Governance approval **is granted**
- Ethics and/or IRB approval is obtained, if required, and
- Separate consent for treatment restart/rechallenge is signed by the subject

Refer to Appendix 10 for full guidance.

7 Adverse Event Reporting

The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

7.1 Definitions

ADVERSE EVENT (EXPERIENCE): Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.

Events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE) unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae.

"Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE.

Events that **do not** meet the definition of an AE include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition

SERIOUS ADVERSE EVENT – A serious adverse event is any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

   NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalisation or prolongation of existing hospitalisation

   NOTE: In general, hospitalisation signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious.

   Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity

   NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

g. All events of possible drug-induced liver injury with hyperbilirubinaemia defined as ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct) (or ALT ≥ 3xULN and INR>1.5, if INR measured) termed 'Hy's Law' events (INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants).

NOTE: bilirubin fractionation is performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin ≥ 2xULN, then the event is still reported as an SAE. If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury.

7.2 Reporting Adverse Events to the Sponsor

7.2.1 Adverse Events of Special Interest

All adverse events of special interest, AESIs, (see Section 8.5.1 for details) that are identified from the start of study medication (Day 0) through Week 52 and regardless if study agent is discontinued early will be recorded on the Adverse Event Case Report Form (AE eCRF). All deaths will be recorded as an outcome from the event that is considered to be the primary event leading to death. All data fields on the AE eCRF should be completed.

7.2.2 Serious Adverse Events

Serious Adverse Events (SAEs) that occur from the start of study agent at Day 0 through Week 52 and regardless if study agent is discontinued early must be recorded on the SAE eCRF within 24 hours of site personnel becoming aware of a SAE, regardless of expectedness. All fields of the SAE eCRF should be completed, but completion of the report should not be held until all information is available. Follow-up information and corrections should be added to the SAE eCRF within 24 hours of site personnel becoming aware of the follow-up information as described in the ePharmaSolutions document portal.

SAEs that occur after Week 52 (or 4 weeks after the last dose of IP if a subject has withdrawn consent to participate in the first year monthly study visits) and that are assessed by the investigator as possibly related to study agent taken the first year must be reported to the Sponsor as outlined in the ePharmaSolutions document portal.

Prior to study drug administration, any SAE assessed as related to study participation (e.g., protocol mandated procedures, invasive tests) will be recorded on the SAE worksheet and reported as described above from the time a subject consents to participate in the study. Pre-treatment SAEs will not be documented on the SAE eCRF.

7.3 Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) resulting in neurological deficits, including fatal cases, has been reported in SLE patients receiving immunosuppressant pharmacotherapy, including belimumab. A diagnosis of PML should be considered in any subject presenting with new-onset or deteriorating neurological signs and symptoms. The subject should be referred to a neurologist or other appropriate specialist for evaluation. If PML is confirmed, study agent should be discontinued and consideration should be given to stopping immunosuppressant therapy.

If PML is suspected, this should be immediately reported to the Medical Monitor. The appropriateness of continuing study agent, while the case is being assessed, should be discussed.

7.4 Suicidality Assessment

Some autoimmune diseases have an increased risk of suicidal behavior and/or ideation (Bachen, 2009; Timonen, 2003; Stenager, 1992). In order to objectively assess suicidality in belimumab clinical programs the C-SSRS (Appendix 4 and Appendix 5) will be utilized to collect information on suicidal behavior and ideation. 'Baseline' C-SSRS (Appendix 4) will be used at screening ONLY; whereas, 'Since Last Visit' C-SSRS (Appendix 5) will be used at all other designated study visits. SLE patients have an increased prevalence of mood and anxiety disorders compared with the general population and disease activity may contribute to this higher risk. The incidence of major depressive disorder (MDD) among SLE patients has been reported to be as high as 47% (Bachen, 2009). Since active SLE and MDD may increase the risk of suicidal ideation or behavior before or during clinical studies, subjects participating in this study will be assessed for suicidality at every visit.

Subjects who answer "yes" to any suicidal behavior or "yes" to suicidal ideation questions 4 or 5 on the C-SSRS should be referred to appropriate psychiatric care and prompts the completion of a SAE worksheet. The medical monitor should be notified when these events occur. In addition, a "yes" to any suicidal behavior or "yes" to suicidal ideation questions 3, 4, or 5 on the C-SSRS prompts the completion of a Possible Suicidality Related History Questionnaire (PSRHQ) eCRF (PSRHQ, only the first time this condition is met), and a Possible Suicidality Related Questionnaire (PSRQ) eCRF at all times this condition is met.

Baseline/Screening and during treatment (Since Last Visit) assessment of suicidality will be performed during the blinded portion of this study using C-SSRS (refer to Appendix 4 and Appendix 5 for C-SSRS). The C-SSRS is a brief measure which is designed to assess severity and change of suicidality by integrating both behavior and ideation [Posner, 2007]. The C-SSRS is administered by a qualified clinician and is designed to address the need for a

summary measure to track change in the severity/density of suicidality across both clinical settings and treatment trials. It assesses intensity of ideation (a potentially important marker of severity) by specifically asking about frequency, duration, intrusiveness, controllability, and deterrents. In addition, it captures both the modal and most severe forms of ideation. The C-SSRS is to be completed by the investigator or his/her qualified designee at every visit during the blinded portion of the study.

7.4.1.1 Possible Suicidality Related Questionnaire (PSRQ)

The investigator will be prompted to complete the PSRQ (in addition to the AE, SAE pages, and PSRHQ as appropriate) if a "yes" response is given to any suicidal behavior or a "yes" response to suicidal ideation questions 3, 4 or 5 on the C-SSRS. If the adverse event meets the definition of an SAE, which includes a "yes" answer to any suicidal behavior or a "yes" to suicidal ideation questions 4 or 5 on the C-SSRS, the site must ensure that there are no significant discrepancies between the PSRQ and SAE.

7.5 Reporting a Pregnancy

Pregnancies must be reported to the Drug Safety designee within 24 hours of the site becoming aware of a pregnancy in a subject. All pregnancies that are identified from the start of study agent through 16 weeks following the last dose of study agent should be reported. All pregnancies are tracked up to term or delivery following the last study agent treatment. When pregnancy is reported, HGS Drug Safety sends an acknowledgement memorandum to the principal investigator along with a Pregnancy Assessment Form. A Pregnancy Assessment Form must be completed every 3 months until live birth, elective termination of the pregnancy, or miscarriage. The site is responsible for following the subject's pregnancy to final outcome.

Pregnancies are not considered adverse events. Complications or medical problems associated with a pregnancy are considered AEs and may be SAEs. Complications or medical problems are reported as AEs/SAEs according to the procedure described in Section 7.2.

7.6 Investigator Evaluation of Adverse Events

The Investigator will evaluate all adverse events with respect to seriousness (criteria for seriousness are listed in Section 7.1), severity (intensity), and causality (relationship to study agent). The investigator will make an assessment of intensity based on the Division of Microbiology and Infectious Diseases (DMID) Adverse Event Severity Grading Tables (see Appendix 7) where possible:

SEVERITY

Grade 1 - Mild	An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities (Grade 1 DMID).
Grade 2 - Moderate	An event that is sufficiently discomforting to interfere with everyday activities (Grade 2 DMID).
Grade 3 - Severe	An event that prevents normal everyday activities (Grade 3 or 4 DMID).
Not applicable	Those event(s) where intensity is meaningless or impossible to determine (i.e., blindness and coma).

An AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

CAUSALITY

The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE. A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated. The investigator will also consult the IB and/or Product Information, for marketed products, in the determination of his/her assessment.

For each AE/SAE the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.** The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

7.7 Follow-Up of Adverse Events of Special Interest and Serious Adverse Events

AESIs (see Section 8.5.1 for details) and SAEs that occur from the start of study agent administration (Day 0) through Week 52 are reported.

After the initial AESI/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All AESIs/SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up. Follow-up of AESI/SAE reports applies to all subjects, including those withdrawn prematurely.

7.8 Reporting Serious Adverse Events to the Regulatory Authorities and Institutional Review Boards/Ethics Committees

All SAEs that are considered by the sponsor to be unexpected and related to belimumab will be reported by the sponsor or designee as expedited (eg, 15-Day) reports to the appropriate regulatory authorities AND to all participating investigators (exceptions discussed below). In addition, the sponsor or designee follows all applicable local and national regulatory requirements regarding safety reporting. Each investigator must also comply with the applicable regulatory requirements related to the reporting of SAEs to the IRBs/IECs responsible for reviewing the study at their site, as well as the regulatory authority(ies) (if applicable).

All SAEs, including disease-related events that meet the definition of a SAE (discussed below), will be monitored by treatment group by an independent DMC (Section 8.3). Investigators, and IRBs/IECs will be notified of the outcome of each DMC meeting, and any recommendations made.

The following conditions (preferred terms; MedDRA v.14.0) are disease-related events that can occur in the study population regardless of belimumab exposure. When these conditions meet the definition of a SAE (ie, when the event is more severe than expected for the subject's SLE condition and meets the regulatory definition of being an SAE), they must be reported to the sponsor within 24 hours of site personnel becoming aware as described in Section 7.2. The sponsor will not submit these events as expedited reports to regulatory authorities, investigators, or IRBs/IECs (unless considered by the sponsor to be related to study agent).

Butterfly rash
Cutaneous lupus erythematosus
Glomerulonephritis membranoproliferative
Glomerulonephritis membranous
Glomerulonephritis proliferative
Lupus encephalitis
Lupus endocarditis
Lupus enteritis
Lupus hepatitis
Lupus myocarditis
Lupus nephritis
Lupus pancreatitis
Lupus pneumonitis
Lupus vasculitis
Nephritic syndrome
Nephritis
Neuropsychiatric lupus
Pericarditis lupus
Peritonitis lupus
SLE arthritis
Systemic lupus erythematosus
Systemic lupus erythematosus rash

In addition, AESI that are study endpoints (Section 8.5.1) generally will not be submitted as expedited reports to regulatory authorities or participating investigators. Specifically, serious infections, malignancies (including NMSC), serious psychiatric events suggesting serious mood disorders/anxiety, suicide, serious infusion and hypersensitivity reactions, and all-cause mortality will not be reported to regulatory authorities or participating investigators as expedited single case reports. These events will be monitored by treatment group by an IDMC (Section 8.3). Investigators will be notified of the outcome of each IDMC meeting, and any recommendations made.

7.9 Regulatory Reporting Requirements for SAEs

Prompt notification of SAEs by the investigator to the Sponsor is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. The Sponsor will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and the Sponsor's policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements

8 Endpoints and Statistical Analysis

8.1 General Statistical Considerations

This main purpose of this study is to provide an evaluation of the difference in the rates of all prespecified AESI and all cause mortality between the belimumab and the placebo groups with a 2-sided 95% confidence interval (CI). SAEs will be analyzed descriptively only.

Safety analyses will be performed on the as-treated population defined as all subjects who are randomized and received at least 1 dose of study agent, grouped according to the treatment that was received for >50% of doses. Secondary efficacy endpoints will be analyzed using the ITT population, grouped according to the treatment that a subject was randomized to receive, regardless of the actual treatment received.

The final analysis for the 52-week study will be performed when all the data have been collected, verified and validated for all subjects through the Week 52 visit.

An interim analysis will be conducted once at least 2000 randomized subjects have completed through Week 52. The interim analysis is solely for monitoring patients' safety and reporting

event rates to health authorities. It will be descriptive in nature and no comparative statistical inferences for claims will be made. Therefore, there will be no adjustment to Type I error for the interim or the final analyses. To minimize bias and to maintain data integrity, the interim analysis will be performed by a statistician who is not affiliated with the study conduct. Similarly, sponsor staff who have access to the interim results will not be involved in subject level monitoring of the study. Site personnel, investigators, and subjects will remain blinded until the study is complete and the final results are made public.

8.2 Randomization Procedure and Assignment to Treatment Groups

Once subjects have consented, have undergone all screening procedures and have been determined to be eligible for the study, they will be randomly assigned (via an interactive web response system) to 1 of 2 treatment groups (10 mg/kg belimumab or placebo) in a 1:1 ratio. The randomization will be stratified for region (US/Canada vs Central America/South America/Mexico vs Europe/Australia/Israel vs Asia), SELENA SLEDAI score (≤ 9 vs ≥ 10), and steroid dose (≤ 7.5 mg/day vs > 7.5 mg/day prednisone or equivalent).

8.3 Independent Data Monitoring Committee (IDMC)

An IDMC will review unblinded safety data for the study on an ongoing basis until the data are locked and analyzed. The IDMC will include at least 3 physicians, and a statistician, none of whom are affiliated with the sponsor. The first IDMC data review meeting will after approximately 500 are enrolled or 6 months from randomization of the first patient, whichever is first. After initial review, the IDMC will review the data approximately every 6 months. Events to be monitored during the safety review will include at a minimum all serious adverse events (including deaths, serious psychiatric events, and serious infections), opportunistic infections (serious and nonserious), malignancies (including NMSC), and serious infusion and hypersensitivity reactions. Investigators and IRBs/IECs will be notified of the outcome of each IDMC meeting.

The IDMC will receive information within 72 hours of the sponsor or designee receiving notification of all SAEs that are life threatening or result in death. Other SAEs will be provided monthly to the IDMC.

8.4 Sample Size Rationale

It was originally planned that a target of 5,000 SLE subjects would be enrolled in this safety study. The sample size was based on the feasibility of enrolling a large number of SLE subjects in a global trial that would provide a reasonable estimate for mortality and other AESI rates. The study design was designed to allow the difference in mortality rates between the placebo and the belimumab treated groups to be established with a 95% confidence interval (CI) of ± 0.46% (ie, within -0.46% and 0.46%), assuming the estimated first year mortality rate was the same 0.68% in the 2 treatment groups. The estimated reference AE mortality rates were based on the annual AE mortality rates in the pooled primary safety database in SLE subjects (integrated database of LBSL02 [placebo-controlled treatment phase only], HGS1006-C1056, and HGS1006-C1057).

8.4.1 Sample Size Re-Estimation

Following the completion of 2 additional placebo-controlled trials (BEL112341/C1115, BEL113750), revised mortality estimates based on data from all 5 of the completed studies were as follows: 0.504% (6/1,190 for the placebo group) and 0.564% (14/2,484 for the belimumab group) with a delta of 0.060%.

Using a conservative revised mortality rate of 0.564%, the 95% CI for a 4,000 subject sample size with 1:1 randomization was also ±0.46%. As a result, given the revised mortality estimate, a sample size of 4,000 subjects would not result in any loss of precision (i.e., the width of the 95% CI remains unchanged). Therefore, agreement was reached with regulatory authorities to reduce the sample size from 5,000 to 4,000 subjects.

8.5 Endpoints and Analysis

8.5.1 Safety Endpoint Definitions and Measurements

The table below describes the safety endpoints and measures collected in the study. All events shown in the table will be collected.

All-cause mortality
Serious Infections (including serious opportunistic infections and any event of TB or TB reactivation)
Non-serious opportunistic infections and other infections of interest (Appendix 2)
Malignancies (excluding NMSC)
Non-melanoma skin cancers
Psychiatric events suggesting serious mood disorders and anxiety
Suicidality (using C-SSRS; Appendix 4 and Appendix 5)
Serious Infusion and Hypersensitivity Reactions
All SAEs

8.5.2 Analysis of Safety Endpoints

Mortality and AESI will be analyzed using an estimation paradigm. The difference in the rates of all prespecified AESI and all cause mortality, between the belimumab and the placebo groups will be evaluated with a 2-sided 95% CI. Deaths will also be described in detail, including, in the belimumab group, assessment of relationship to belimumab treatment.

For all cause mortality, the hazard ratio (and its 95% CI) for belimumab vs placebo will be estimated using the Cox proportional hazard model, without adjustment for baseline randomization factors. The time to death will be censored at the last follow-up by the end of the study for subjects who are alive.

SAEs will be analyzed descriptively only. The frequency and rate of serious adverse events will be tabulated by MedDRA system organ class (SOC) and preferred term. The SAE rates may also be reported adjusted for subject years.

8.5.3 Efficacy Endpoint Definitions and Measurements

The major efficacy endpoint is:

- Percent of subjects whose average prednisone (or equivalent) dose has been reduced by ≥ 25% from baseline to ≤ 7.5 mg/day during Weeks 40 through 52 (in the subgroup of subjects receiving > 7.5 mg/day of prednisone (or equivalent) at baseline).

Other efficacy endpoints include:

- Use of immunomodulatory medications to treat SLE.
- Number of hospitalizations per patient.
- Percent of patients hospitalized.

SLICC/ACR Damage Index will be recorded at baseline and at Week 52 to permit assessment of accrual of damage in subjects who may be followed a subsequent study.

8.5.4 Analysis of Major Efficacy Endpoint

The percent of subjects with average prednisone (or equivalent) dose that has been reduced by ≥ 25% from baseline to ≤ 7.5 mg/day during Weeks 40 through 52 will be compared between the belimumab and the placebo groups using a logistic regression model, adjusted for baseline prednisone (or equivalent) dose level, baseline SELENA SLEDAI score (≤ 9 vs ≥ 10), and region (US/Canada or Central America/South America/Mexico or Europe/Australia/Israel or Asia). The analysis will be performed on subjects who were using prednisone (or equivalent) at a dose > 7.5 mg/day at baseline. In the analysis, all subjects who drop out and/or add new immunomodulatory agents before the Week 52 visit will be considered having no steroid reduction. However, switching immunomodulatory agents for toxicity reasons or lack of availability (eg, no longer manufactured or no longer reimbursed) is permitted and will not be imputed as no steroid reduction. To examine the robustness of the results, a sensitivity analysis of the steroid reduction may be performed without considering any information related to the use of new immunomodulatory agents.

Analysis of other efficacy endpoints will be described in the analytical plan.

9 Pharmacogenetics (PGx)

This is an optional sub-study. The IEC/IRB and, where required, the applicable regulatory agency must approve the PGx assessments before these can be conducted at the study site. The approval(s) must be in writing and clearly specify approval of the PGx assessments (ie, approval of Appendix 7). In some cases, approval of the PGx assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate that approval of the PGx assessments is being deferred and the study, except for PGx assessments, can be initiated. When PGx assessments are not approved, then approval for the rest of the study will clearly indicate this and that PGx assessments will not be conducted.

In consenting subjects, a blood sample for PGx research will be drawn to better characterize genetic variability (eg, HLA typing) that may affect efficacy or safety endpoints. Information regarding PGx research is included in Appendix 7.

10 Study Administration

This study will be jointly sponsored by Human Genome Sciences (HGS) and GlaxoSmithKline (GSK). HGS will lead the operational conduct of this study on a world-wide basis working with contract research organizations.

10.1 Informed Consent

A copy of the proposed informed consent document must be submitted to the sponsor or designee for review and comment prior to submission to the reviewing IRB/IEC. The consent form must be approved by the IRB/IEC and contain all elements required by national, state, local, and institutional regulations or requirements. In the event that local regulations/laws require a Privacy Authorization this will be included as part of the informed consent process.

It is the responsibility of the investigator to provide each subject with full and adequate verbal and written information using the IRB/IEC approved informed consent document(s), including the objective and procedures of the study and the possible risks involved before inclusion in the study. Each subject must voluntarily provide written informed consent (including consent for the use and disclosure of research-related health information). The consent must be obtained prior to performing any study-related procedures that are not part of normal patient care, including screening and changes in medications including any washout of medications. A copy of the signed informed consent must be given to the study subject.

10.2 Institutional Review Board Review/Independent Ethics Committee Review and Approval

The investigator or sponsor (as appropriate per national regulations) shall assure that an IRB/IEC, constituted in accordance with the ICH Guideline for Good Clinical Practice (GCP), will provide initial and continuing review of the study.

Prior to shipment of the study agent and enrollment of study subjects, documented IRB/IEC approval of the protocol, informed consent form, and any advertisement for subject recruitment must be obtained and provided to the sponsor or designee.

The IRB/IEC must also be informed of all protocol amendments prior to implementation. The investigator must provide reports of any change in research activity (ie, the completion, termination, or discontinuation of a study) to the IRB/IEC.

10.3 Protocol Compliance

Except for a change that is intended to eliminate an apparent immediate hazard to a study subject, the protocol shall be conducted as described. Any such change must be reported immediately to the sponsor and to the IRB/IEC.

10.4 Protocol Revisions

Protocol amendments will be prepared and approved by the sponsor. All protocol amendments will be signed by the investigator and submitted to the IRB/IEC for review prior to implementation. Documentation of IRB/IEC approval must be forwarded to the sponsor or designee. If an amendment significantly alters the study design, increases potential risk to the subject or otherwise affects statements in the informed consent form, the informed consent form must be revised accordingly and submitted to the IRB/IEC for review and approval. The approved consent form must be used to obtain informed consent from new subjects prior to enrollment and must be used to obtain informed consent from subjects already enrolled if they are affected by the amendment.

10.5 Data Collection and Management

The investigator is responsible for maintaining accurate, complete, and up-to-date records for each subject. The investigator is also responsible for maintaining any source documentation related to the study, including any films, tracings, computer discs, or tapes.

The anonymity of participating subjects must be maintained. For data collection and management purposes, subjects are to be identified by a subject number only. Documents that identify the subject beyond subject number will not be submitted to the sponsor (eg, the signed informed consent document; subject initials) and must be maintained in strict confidence by the investigator, except to the extent necessary to allow auditing by the regulatory authorities, study monitor, or sponsor representatives.

Site personnel record all data for each study subject through electronic case report forms (eCRFs) using an Electronic Data Capture (EDC) system provided and approved by the sponsor. Refer to the Study Procedures Manual for additional information regarding eCRFs that will be used as source documentation. Sites must complete the eCRFs in a timely manner and the investigator must promptly review the completed eCRFs for each subject. As the person ultimately responsible for the accuracy of all eCRF data, the investigator must sign the Investigator's Statement in each subject's eCRF.

The EDC system automatically generates queries resulting from the computer checks embedded into the system, so as to ensure accuracy, quality, consistency, and completeness of the database. Manual queries resulting from review by monitors, medical coders, and other Data Management staff are also generated from within the EDC system, where they are tracked. Sites resolve the queries and correct the entered data when necessary. Every change to data is captured in the EDC system audit trail. Upon completion of the study, or after reaching a pre-specified point in the study, Data Management will lock the database and generate the SAS datasets necessary for data analysis and reporting. Upon completion of the study, each site will be provided with a compact disk containing the eCRFs for each of their subjects.

10.6 Study Monitoring

The study sponsor or designee will monitor the study. Study monitors representing the sponsor will visit study sites throughout the trial. The sponsor will review eCRFs and compare a sample of them with source documents to verify accurate and complete collection of data and confirm that the study is being conducted according to the protocol. Auditors representing the sponsor may also similarly evaluate the study and its monitors. For these purposes, the investigator will make eCRFs and source documents available when requested.

In addition, the study may be evaluated by representatives of the national regulatory authorities, who will also be allowed access to study documents. The investigators should promptly notify Human Genome Sciences of any audits they have scheduled with any regulatory authority.

10.7 Drug Accountability

Upon receipt, the investigator or their designee, is responsible for taking an inventory of the study agent, including any buffers or diluents. A record of this inventory must be kept and usage must be documented on study agent inventory forms provided by the sponsor.

Study agent inventory forms will be examined and reconciled by a sponsor monitor, or designee. At the end of the study, all used and unused study agent must be accounted for on a study agent accountability form provided to the investigator by HGS or its designee.

10.8 Retention of Records

The investigator shall retain all records and source documents pertaining to the study, including any films, tracings, computer discs, or tapes. They will be retained for the longer of the maximum period required by the country and institution in which the study is conducted, or the period specified by the sponsor at the time the study is completed, terminated, or discontinued.

If the investigator leaves the institution, the records shall be transferred to an appropriate designee who accepts the responsibility for record retention. Notice of such transfer shall be documented in writing and provided to the sponsor.

10.9 Financial Disclosure

The investigator and all sub-investigators will provide the sponsor sufficient and accurate information on financial interests (proprietary or equity interests, payments exclusive of clinical trial costs) to allow complete disclosure to regulatory authorities. The investigators shall promptly update this information if any relevant changes occur during the course of the investigation and for a period of 1 year following study completion.

10.10 Publication Policy

This study is being conducted as part of a multi-center clinical study. Data from all sites participating in the multi-center clinical study will be polled and analyzed. The investigators

acknowledge that an independent, joint publication is anticipated to be authored by the investigators of the multi-center study and the sponsor's representatives. Neither the participating institutions nor the principal investigators shall publish or present the results of the study prior to the publication of the multi-center study publication. The investigators agree that the sponsor will be the coordinator and arbitrator of all multi-center study publications. For multi-center trials, no investigator will be authorized to publish study results from an individual center until the earlier of the multi-center trial results are published or 12 months after the end or termination of the multi-center trial at all sites.

The investigator shall submit a copy of any proposed publication, manuscript, abstract, presentation or other document with respect to this study to the sponsor for review and comment at least 60 days prior to its submission for publication or presentation. No publication or presentation with respect to the study shall be made unless and until all of the sponsor's comments on the proposed publication or presentation have been considered and any information determined by the sponsor to be confidential information has been removed. If requested in writing by the sponsor, the investigator shall withhold material from submission for publication or presentation for an additional 60 days to allow for the filing of a patent application or the taking of other measures to establish and preserve the sponsor's proprietary rights.

10.11 Study or Study Site Termination

If the sponsor, the investigator, IRB/IEC, or a regulatory authority discovers conditions arising during the study that indicate that the study should be halted or that the study center should be terminated, this action may be taken after appropriate consultation between the sponsor and the investigator. Conditions that may warrant termination of the study include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study.

The study site may warrant termination under the following conditions:

- Failure of the investigator to enroll subjects into the study at an acceptable rate.
- Failure of the investigator to comply with pertinent regulatory authority regulations.
- Submission of knowingly false information from the research facility to HGS, study monitor, or the regulatory authority.
- Insufficient adherence to protocol requirements.

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List of Appendices

Appendix 1 American College of Rheumatology (ACR) Criteria for SLE

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

Appendix 2 Infections of Interest

"Infections of Interest" include opportunistic infections and other infections of interest generally not considered opportunistic. Opportunistic infections are a subset of infections that are caused by organisms that usually do not cause disease in immunocompetent individuals but which may cause illness, or more severe illness, when the immune system is suppressed. Since there are no general guidelines for labeling pathogens as opportunistic without considering the host's immune condition, identification of opportunistic infections and other infections of interest in this study is based on the following list of pathogens which when present may indicate immune suppression in a subject. These pathogens and infections in general are rarely observed in immunocompetent individuals and will be considered opportunistic. Pathogens considered to cause opportunistic infections and other infections of interest include but are not limited to the following:

Acinetobacter infection

Aspergillosis

Blastomycosis, extrapulmonary

Candidiasis of esophagus, bronchi, trachea, or lungs

Coccidioidomycosis, dissemintaed or extrapulmonary

Cryptococcosis, extrapulmonary

Cryptosporidiosis infection, chronic intestinal (> 1 month duration)

Cytomegalovirus disease (other than liver, spleen, or nodes)

Herpes simplex bronchitis, pneumonitis, or esophagitis

Disseminated herpes zoster or involving at least 2 distinct episodes (see other infections of interest below)

Histoplasmosis disseminated or extrapulmonary

Human polyomavirus infection

Isosporiasis, chronic intestinal (> 1 month's duration)

Listeriosis

Mycobacterium avium complex or M. Kansasii, disseminated or extrapulmonary

Mycobacterium infections, other species or unidentified species, disseminated or extrapulmonary (eg, M. haemophilium, M. fortuitum, or M. marinum)

Nocardiosis

Polyomavirus (JC virus or BK virus)-associated nephropathy (including progressive multifocal leukoencephalopathy)

Pneumocystis jiroveci infection

Toxoplasmosis of brain

Other infections of interest that will be recorded in this study, but which are not generally considered opportunistic, include:

Mycobacterium tuberculosis, any site, latent or active

Salmonella sepsis

Hepatitis B

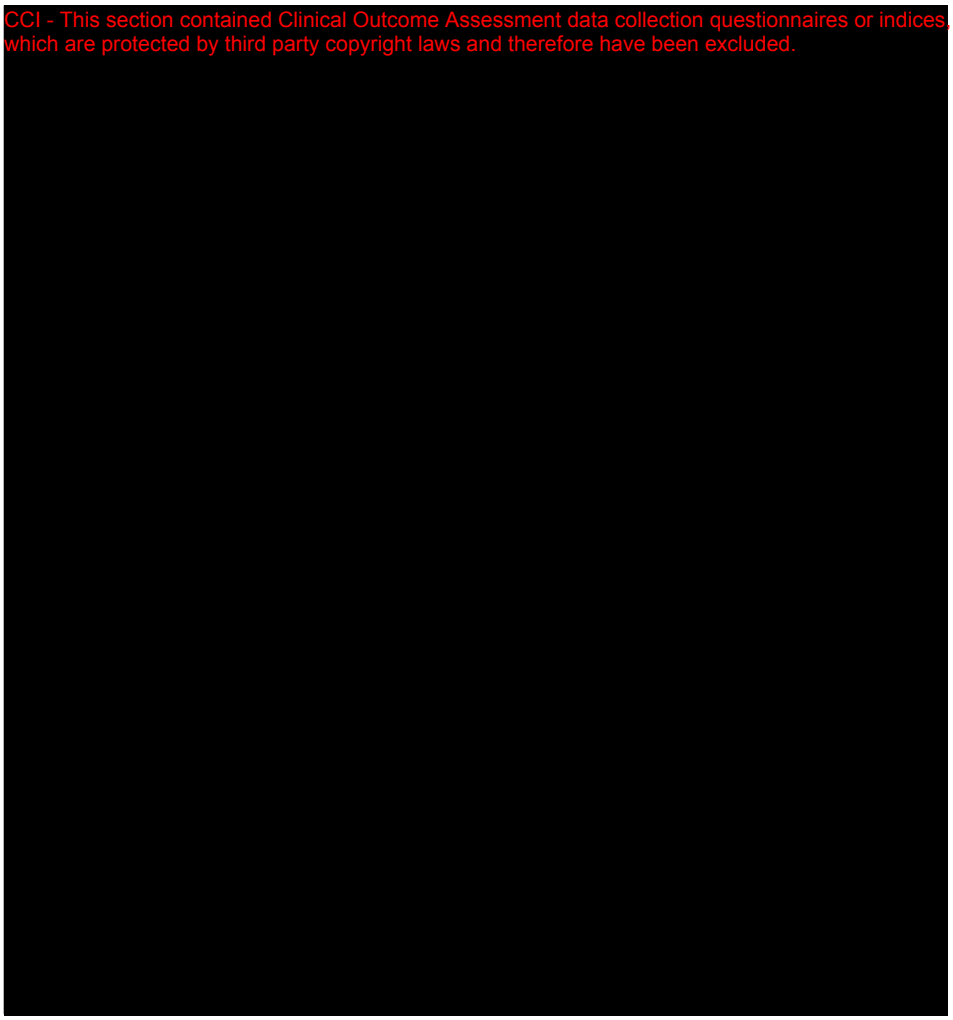
Hepatitis C

All other (ie, non-disseminated or single episode) herpes zoster (shingles)

Appendix 3 SLICC/ACR Damage Index

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

Appendix 4 Columbia- Suicide Severity Rating Scale (C-SSRS) Baseline/Screening



Appendix 6 SELENA SLEDAI Score

Score if descriptor is present at time of visit or in the preceding 30 days.

Wgt.	Descriptor	Definition
8	Seizure	Recent onset (last 30 days). Exclude metabolic, infectious drug cause, or seizure due to past irreversible CNS damage.
8	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Exclude uremia and drug causes.
8	Organic Brain Syndrome	Altered mental function with impaired orientation, memory or other intellectual function with rapid onset and fluctuating clinical features. Include clouding of consciousness with reduced capacity to focus and inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious, or drug causes.
8	Visual Disturbance	Retinal and eye changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudate of hemorrhage in the choroid, optic neuritis, scleritis or episcleritis. Exclude hypertension, infection, or drug causes.
8	Cranial Nerve Disorder	New onset sensory or motor neuropathy involving cranial nerves. Include vertigo due to lupus.
8	Lupus Headache	Severe persistent headache: may be migrainous, but must be non-responsive to narcotic analgesia.
8	CVA	New onset of CVA(s). Exclude arteriosclerosis or hypertensive causes.
8	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.
4	Arthritis	More than 2 joints with pain & signs of inflammation (ie, tenderness, swelling or effusion).
4	Myositis	Proximal muscle aching/weakness associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.
4	UrinaryCasts	Heme-granular or red blood cell casts.
4	Hematuria	> 5 red blood cells/high power field. Exclude stone, infection, or other causes.
4	Proteinuria	New onset or recent increase of more than 0.5 g/24 hours.
4	Pyuria	> 5 white blood cells/high power field. Exclude infection.
2	Rash	New or ongoing inflammatory lupus rash.
2	Alopecia	New or ongoing abnormal, patchy or diffuse loss of hair due to active lupus.
2	Mucosal Ulcers	New or ongoing oral or nasal ulcerations due to active lupus.
2	Pleurisy	Classic and severe pleuritic chest pain or pleural rub or effusion or new pleural thickening due to lupus.
2	Pericarditis	Classic and severe pericardial pain or rub or effusion, or electrocardiogram confirmation.
2	Low Complement	Decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory.
2	Increased DNA Binding	> 25% binding by Farr assay or above normal range for testing laboratory.
1	Fever	> 38°C. Exclude infectious cause.
1	Thrombocytopenia	< 100,000 platelets/mm^3
1	Leukopenia	< 3,000 white blood cells/mm^3. Exclude drug causes.
	TOTAL SCORE	**(Sum of weights next to descriptors marked present)**

Adapted from:

Bombardier C, Gladman DD, Urowitz MB, et al. Derivation of the SLEDAI: a disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. Arthritis Rheum 1992; 35(6):630-40.

Touma Z, Urowitz MB, Gladmann DD. SLEDAI-2K for a 30-day window. Lupus 2010; 19:49-50.

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Appendix 7 Pharmacogenetic Research

Background

Pharmacogenetics (PGx) is the study of variability in drug response due to hereditary factors in different populations. There is increasing evidence that an individual's genetic composition (ie, genotype) may impact pharmacokinetics, pharmacodynamics (relationship between concentrations and pharmacologic effects or the time course of pharmacologic effects) and/or clinical outcome (in terms of efficacy and/or safety and tolerability).

A key component to successful PGx research is the collection of samples during the conduct of clinical studies.

Research Rationale

Blood samples for pharmacogenetics will be drawn as described in Section 9. Collection of whole blood samples, even when no *a priori* hypothesis has been identified, may enable PGx analyses to be conducted if there is unexplained or unexpected variation in response to belimumab.

If at any time it appears there is potential variability in response in this clinical study or in a series of clinical studies with belimumab that may be attributable to genetic variations of subjects, the following objectives may be investigated:

- Relationship between genetic variants and the pharmacokinetics of belimumab.
- Relationship between genetic variants and safety and/or tolerability of belimumab.
- Relationship between genetic variants and efficacy of belimumab.

Study Population

Any subject who has given informed consent to participate in the clinical study, has met all the entry criteria for the clinical study, and receives belimumab may take part in the PGx research.

Subject participation in the PGx research is voluntary and refusal to participate will not indicate withdrawal from the clinical study. Refusal to participate will involve no penalty or loss of benefits to which the subject would otherwise be entitled.

Informed Consent

Subjects who do not wish to participate in the PGx research may still participate in the clinical study. PGx informed consent must be obtained prior to any blood being taken for PGx research.

Study Assessments and Procedures

In addition to any blood samples drawn for the clinical study, a whole blood sample (~10 mL) will be collected for the PGx research at baseline. The PGx sample is labeled (or coded) with a study specific number that can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number). The blood sample will be taken on a single occasion unless a duplicate sample is required due to inability to utilize the original sample. The blood samples should be drawn on Day 0 (baseline), provided informed consent for PGx research has been obtained from the subject, but the sample may be taken at any time while the subject is participating in the clinical study.

If deoxyribonucleic acid (DNA) is extracted from the blood sample, the DNA will be subjected to sample quality control analysis. This analysis will involve the genotyping of several genetic markers to confirm the integrity of individual samples. If inconsistencies are noted in the analysis, then those samples may be destroyed.

The need to conduct PGx analysis may be identified after a study (or set of studies) of belimumab has been completed and the study data reviewed. In some cases, the samples may not be studied.

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study or the sponsor may destroy the samples sooner. The sponsor or those working with the sponsor (for example, other researchers or a contract lab) will use samples collected from the study for the purpose stated in this protocol and in the subject informed consent form.

Subjects may request their sample to be destroyed at any time.

Subject Withdrawal from Study

If a subject who has consented to participate in PGx research and has a sample taken for PGx research withdraws from the clinical study for any reason other than lost to follow-up, the subject will be given the following options:

1. The sample is retained for PGx research.
2. The sample is destroyed.

If a subject withdraws consent from the PGx research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by the sponsor and maintain the documentation in the site study records. In either case, the sponsor will only use study information collected/generated up to that point.

Screen and Baseline Failures

If a blood sample for PGx research has been collected and it is determined that the subject does not meet the entry criteria for participation in the clinical study, then the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by the sponsor and maintain the documentation in the site study records.

Pharmacogenetic Analyses

Specific sections of DNA may be selected from areas of the genome (ie, candidate genes). The candidate genes could include the drug target, the drug target pathway, drug metabolizing enzymes, genes associated with mechanisms underlying adverse events, and genes associated with the study disease.

In addition, a genome-wide scan or large scale sequencing of polymorphic markers located across the genome may be implemented. This approach is often employed when potential genetic effects are not well understood.

Other new technologies may be developed to help us better study and understand genetic variants associated with drug response.

Continuing research may identify other enzymes, transporters, proteins, or receptors that may be involved in response to belimumab. The genes that may code for these proteins may also be studied.

Components of the PGx analysis may include:

- Hardy-Weinberg Equilibrium testing

  The genotypic frequencies of each polymorphism will be evaluated for conformity to those expected under normal conditions by employing Hardy-Weinberg Equilibrium testing.

- Comparison of Demographic and Baseline Characteristics by Genotype

  Differences in baseline clinical characteristics and potential contributing covariates may be summarized and compared among genotype (or haplotype) subgroups.

- Evaluation of Genotypic Effects

  Analyses may be carried out to evaluate the degree of association between subject's genotype (or haplotype) and selected parameters (eg, pharmacokinetics, disease activity and safety). Where such genotypic tests are inappropriate (eg, where the number of marker genotypes is too large and/or the frequency of individual genotypes too small), allelic tests may be conducted. Allelic tests evaluate whether the frequency of each marker allele is the same in responders and non-responders.

- Evaluation of Treatment by Genotype and Gene-Gene Interaction

  In addition to evaluating the main effects of the genotypes (haplotypes or alleles) on the selected parameters, the possibility of a treatment group by genotype (haplotype or allele) interaction will also be explored. If appropriate, the joint effects of multiple markers (gene-gene interactions) may also be evaluated.

- Linkage Disequilibrium

  For pairs of polymorphisms, the degree to which alleles from the 2 sites are correlated (linkage disequilibrium) may also be evaluated. If the genotypes at 2 polymorphic sites within a gene are shown to be statistically associated with a response to study agent, the degree of linkage disequilibrium will aid interpretation in that it will indicate the extent to which the 2 sites are exerting independent effects.

- Multiple Comparisons and Multiplicity

  Adjustment to observed p-values may be made to limit erroneous conclusions due to multiple tests when multiple markers are evaluated (especially in the case of a genome scan for association).

- Power and Sample Size Considerations

  The ability to detect differential drug response among genotypes at a polymorphic site depends on the total number of subjects genotyped and the frequency distribution of the different genotypes. Consequently, genotyping analyses are plausible for those polymorphic sites where the number of subjects comprising the genotypic groups is sufficiently large; however, these frequencies will not be known until sufficient samples have been collected and genotyping is complete. These examples show that small sample sizes typically encountered in Phase 1 and Phase 2 studies may be sufficient to identify clinically relevant genetic associations.

Additional analyses may be conducted as necessary.

Provision of Study Results and Confidentiality of Subject's PGx Data

The sponsor may summarize the cumulative PGx research results in the clinical study report or in a separate report. In general, the sponsor does not inform the investigator, subject or anyone else (eg, family members, study investigators, primary care physicians, insurers, or employers) of the PGx research results because the information generated from PGx studies is preliminary in nature, and the significance and scientific validity of the results are undetermined at such an early stage of research, under any circumstance unless required by law.

Appendix 8 Adverse Event Severity Grading Tables

SKIN (INJECTION SITE)	GRADE 1 MILD	GRADE 2 MODERATE[1]	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Induration	< 15mm	15-30 mm	> 30mm	n/a
Erythema	< 15mm	15-30 mm	> 30mm	n/a
Edema	< 15mm	15-30 mm	> 30mm	n/a
Rash at Injection Site	< 15mm	15-30 mm	> 30mm	n/a
Pruritus	slight itching at injection site	moderate itching at injection extremity	itching over entire body	n/a

[1]May be assessed as mild despite the size if event is transient (< 48 hours) with mild discomfort; no medical intervention/therapy required

Modified from DMID Adult Toxicity Tables, 2007

HEMATOLOGY	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hemoglobin	> 9.5-11.0 g/dL	> 8.0-9.5 g/dL	6.5-8.0 g/dL	< 6.5 g/dL
Leukocytes	3000-3999/mm3	2000-2999/mm3	1000-1999/mm3	< 1000/mm3
Absolute Neutrophil Count	1500-1999/mm3	1000-1499/mm3	500-999/mm3	< 500/mm3
Platelets	75,000-99,999/mm3	50,000–74,999/mm3	25,000-49,999/mm3	< 25,000/mm3
Prothrombin Time (PT)	> 1.0-1.25 x ULN*	> 1.25-1.5 x ULN	> 1.5-3.0 x ULN	> 3.0 x ULN
Partial Thromboplastin Time (PTT)	> 1.0-1.66 x ULN	> 1.66-2.33 x ULN	> 2.33-3.0 x ULN	> 3.0 x ULN
Methemoglobin	5.0-10.0 %	10.1-15.0 %	15.1-20.0 %	> 20%

(continued)

*ULN = Upper Limit of Normal.

Modified from DMID Adult Toxicity Tables, 2001

CARDIOVASCULAR	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Cardiac Arrhythmia	-	Asymptomatic/transient; dysrhythmia; no treatment req	Recurrent/persistent dysrhythmia. Symptomatic; treatment req	Unstable dysrhythmia hospitalization and treatment required
Hypotension	Transient orthostatic hypotension, no treatment	Symptoms correctable with oral fluid treatment	IV fluid req, no hospitalization req	Hospitalization req
Hypertension	Transient, increase > 20 mm/Hg; no treatment	Recurrent; chronic increase > 20 mm/Hg, treatment req	Acute treatment req; out patient hospitalization possible	Hospitalization req
Pericarditis	Minimal effusion	Mild/moderate asymptomatic effusion, no treatment	Symptomatic effusion, pain, ECG changes	Tamponade OR pericardiocentesis OR surgery req
Hemorrhage, Blood Loss	-	Mildly symptomatic; no treatment required	Gross blood loss OR 1-2 units transfused	Massive blood loss OR > 2 units transfused

(continued)

Modified from DMID Adult Toxicity Tables, 2001

CHEMISTRIES	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Sodium				
Hyponatremia	130-135 meq/L	123-129 meq/L	116-122 meq/L	< 116 meq/L
Hypernatremia	146-150 meq/L	151-157 meq/L	158-165 meq/L	> 165 meq/L
Potassium				
Hypokalemia	3.0-3.4 meq/L	2.5-2.9 meq/L	2.0-2.4 meq/L	< 2.0 meq/L
Hyperkalemia	5.6-6.0 meq/L	6.1-6.5 meq/L	6.6-7.0 meq/L	> 7.0 meq/L
Phosphate				
Hypophosphatemia	2.0-2.4 mg/dL	1.5-1.9 mg/dL	1.0-1.4 mg/dL	< 1.0 mg/dL
Calcium- (Corrected For Albumin)				
Hypocalcemia	7.8-8.4 mg/dL	7.0-7.7 mg/dL	6.1-6.9 mg/dL	< 6.1 mg/dL
Hypercalcemia	10.6-11.5 mg/dL	11.6-12.5 mg/dL	12.6-13.5 mg/dL	> 13.5 mg/dL
Magnesium				
Hypomagnesemia	1.2-1.4 meq/L	0.9-1.1 meq/L	0.6-0.8 meq/L	< 0.6 meq/L
Albumin				
Hypoalbuminemia	3.00-3.49 g/dL	2.50-2.99 g/dL	2.00-2.49 g/dL	< 2.00 g/dL
Bilirubin (Total)				
Hyperbilirubinemia (Total)	> 1.0-1.5 x ULN	> 1.5-2.5 x ULN	> 2.5-5 x ULN	> 5 x ULN
Glucose				
Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	< 30 mg/dL
Hyperglycemia (nonfasting & no prior diabetes)	116-160 mg/dL	161-250 mg/dL	251-500 mg/dL	> 500 mg/dL
Triglycerides	151-399 mg/dL	400-750 mg/dL	751-1200 mg/dL	> 1200 mg/dL
Creatinine	> 1.0-1.5 x ULN	> 1.5-3.0 x ULN	> 3.0-6.0 x ULN	> 6.0 x ULN

(continued)

Modified from DMID Adult Toxicity Tables, 2001

CHEMISTRIES	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Uric Acid				
Hyperuricemia	7.5-10.0 mg/dL	10.1-12.0 mg/dL	12.1-15.0 mg/dL	> 15.0 mg/dL
Liver Transferases (AST, ALT, and GGT)	1.25-2.5 x ULN	> 2.5-5.0 x ULN	> 5.0-10.0 x ULN	> 10.0 x ULN
Alkaline Phosphatase	1.25-2.5 x ULN	> 2.5-5.0 x ULN	> 5.0-10.0 x ULN	> 10.0 x ULN
Pancreatic Enzymes				
Amylase	> 1.0-1.5 x ULN	> 1.5-2.0 x ULN	> 2.0-5.0 x ULN	> 5.0 x ULN
Pancreatic amylase	> 1.0-1.5 x ULN	> 1.5-2.0 x ULN	> 2.0-5.0 x ULN	> 5.0 x ULN
Lipase	> 1.0-1.5 x ULN	> 1.5-2.0 x ULN	> 2.0-5.0 x ULN	> 5.0 x ULN
*Hypoglobulinemia (IgG)**	550-700 mg/dL	400-549 mg/dL	250-399 mg/dL	< 250 mg/dL

(continued)

*(Goldfarb et al, 2001; Yamani et al, 2001; Eibl and Rosen, 1995).

Modified from DMID Adult Toxicity Tables, 2001

GASTROINTESTINAL	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Nausea	Mild OR transient; reasonable intake maintained	Mod discomfort OR intake decreased for < 3 days	Severe discomfort OR minimal intake for ≥ 3 days	Hospitalization required
Vomiting	Mild OR transient; 2-3 episodes/day OR mild vomiting lasting < 1 week	Mod OR persistent; 4-5 episodes per day; OR vomiting lasting ≥ 1 week	Severe vomiting of all foods/fluids in 24 hours OR orthostatic hypotension OR IV treatment req	Hypotensive shock OR hospitalization required for IV treatment req
Diarrhea	Mild or transient; 3-4 loose stools per day OR mild diarrhea lasting < 1 week	Mod OR persistent; 5-7 loose stools per day or diarrhea lasting ≥ 1 week	Bloody diarrhea; OR orthostatic hypotension OR > 7 loose stools/day OR IV treatment req	Hypotensive shock OR hospitalization req
Oral Discomfort/Dysphagia	Mild discomfort, no difficulty swallowing	Difficulty swallowing but able to eat and drink	Unable to swallow solids	Unable to drink fluids; IV fluids req
Constipation	Mild	Moderate	Severe	Distention with vomiting

(continued)

Modified from DMID Adult Toxicity Tables, 2001

RESPIRATORY	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Cough (for aerosol studies)	Transient; no treatment	Treatment associated cough; inhaled bronchodilator	Uncontrolled cough; systemic treatment req	-
Bronchospasm Acute	Transient; no treatment; FEV1 70% to < 80% (or peak flow)	treatment req; normalizes with bronchodilator; FEV1 50% to < 70% (or peak flow)	No Normalization with bronchodilator; FEV 25% to < 50% (or peak flow), retractions	Cyanosis; FEV1 < 25% (or peak flow) OR intubated
Dyspnea	Dyspnea on exertion	Dyspnea with normal activity	Dyspnea at rest	Dyspnea requiring O2 therapy

URINALYSIS	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Proteinuria:				
Dipstick: Protein	1 +	2-3 +	4 +	Nephrotic syndrome
Spot Urine: Protein:Creatinine Ratio mg/mg	0.2-1.0	> 1.0-2.0	> 2.0-3.5	> 3.5
24 hour Urine: Protein	200 mg - 1g loss/day	> 1-2 g loss/day	> 2-3.5 g loss/day	Nephrotic syndrome OR > 3.5 g loss/day
Hematuria	Microscopic only > 3 - < 10 RBC/hpf	Gross, No clots ≥ 10 RBC/hpf	Gross plus clots OR RBC casts	Obstructive OR transfusion required

(continued)

RBC = red blood cell; hpf = high power field.

Modified from DMID Adult Toxicity Tables, 2001

MISCELLANEOUS	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Fever (oral > 12 hours)	37.7-38.5°C or 100.0-101.5°F	38.6-39.5°C OR 101.6-102.9°F	39.6-40.5°C OR 103-105°F	> 40.5°C OR > 105°F
Headache	Mild; No treatment req	Mod; or non-narcotic analgesia treatment	Severe; OR responds to initial narcotic treatment	Intractable; OR requiring repeated narcotic treatment
Allergic Reaction	Pruritus without rash	Localized urticaria	Generalized urticaria angioedema	Anaphylaxis
Cutaneous/Rash/ Dermatitis	Erythema, pruritus rash OR dry desquamation	Diffuse maculopapular OR dry desquamation	Vesiculation OR moist desquamation ulceration	ANY ONE: mucous membrane involvement, suspected Stevens-Johnson (TEN), erythema multiforme, necrosis req surgery, exfoliative dermatitis
Local Reaction (secondary to parenteral treatment- not vaccination or skin test)	Erythema	Induration < 10 mm OR inflammation OR phlebitis	Induration > 10 mm OR ulceration	Necrosis of skin
Fatigue	Normal activity Reduced < 25%	Normal activity Reduced 25-50%	Normal activity reduced > 50%; cannot work	Unable to care for self

(continued)

Modified from DMID Adult Toxicity Tables, 2001

NEUROLOGIC	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Neuro-cerebellar	Slight incoordination OR dysdiadochokinesia	Intention tremor OR dysmetria OR slurred speech OR nystagmus	Ataxia requiring assistance to walk or arm incoordination interfering with ADLs	Unable to stand
Neuro-psych/ mood	-	none	Severe mood changes requires medical intervention	Acute psychosis requiring hospitalization
Paresthesia (burning, tingling, etc)	Mild discomfort; no treatment needed	Mod discomfort non-narcotic analgesia req	Severe discomfort; OR narcotic analgesia req with symptomatic improvement	Incapacitating; OR not responsive to narcotic analgesia
Neuro-motor	Mild weakness in muscle of feet but able to walk and/or mild increase or decrease in reflexes	Mod weakness in feet (unable to walk on heels and/or toes), mild weakness in hands, still able to do most hand tasks and/or loss of previously present reflex or development of hyperreflexia and/or unable to do deep knee bends due to weakness	Marked distal weakness (unable to dorsiflex toes or foot drop), and mod proximal weakness ie, in hands interfering with ADLs and/or requiring assistance to walk and/or unable to rise from chair unassisted	Confined to bed or wheelchair because of muscle weakness
Neuro-sensory	Mild impairment sensations, (ie, vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution	Mod impairment mod de-sensation, (ie, of vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical.	Severe impairment (dec or loss of sensation to knees or wrists) or loss of sensation of at least mod degree in multiple different body areas (ie, upper and lower extremities)	Sensory loss involves limbs and trunk

(concluded)

Modified from DMID Adult Toxicity Tables, 2001

Appendix 9 Liver Safety Required Actions and Follow up Assessments

Phase III-IV liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Phase III-IV liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria - Liver Stopping Event	
ALT-absolute	ALT ≥ 8xULN
ALT Increase	ALT ≥ 5xULN but <8xULN persists for ≥2 weeks ALT ≥ 3xULN but <5xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5, if INR measured
Cannot Monitor	ALT ≥ 5xULN but <8xULN and cannot be monitored weekly for ≥2 weeks ALT ≥ 3xULN but <5xULN and cannot be monitored weekly for ≥4 weeks
Symptomatic[3]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• Immediately discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the subject until liver chemistries resolve , stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** subject with study treatment unless allowed per protocol and GSK Medical Governance approval **is granted** (refer to Appendix 10) • If restart/rechallenge **not allowed or not granted**, permanently discontinue study treatment and may continue subject in the study for any protocol specified follow up assessments	• Viral hepatitis serology[4] • Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody[5] • Blood sample for pharmacokinetic (PK) analysis, obtained within approximately 1 to 2 weeks after the liver event[6] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH) • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on

MONITORING: **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **<u>For All other criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form **<u>For bilirubin or INR criteria:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). **NOTE: not required in China** • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants.
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia).
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody.
5. If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Le Gal, 2005].
6. PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the study reference manual.

Phase III-IV liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥5xULN and <8xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks. OR ALT ≥3xULN and <5xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks.	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss subject safety. • Subject can continue study treatment • Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If at any time subject meets the liver chemistry stopping criteria, proceed as described above • If ALT decreases from ALT ≥5xULN and <8xULN to ≥3xULN but <5xULN, continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.

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Appendix 10 Liver Safety – Study Treatment Restart or Rechallenge Guidelines Liver

If subject meets liver chemistry stopping criteria do not restart/rechallenge subject with study treatment unless:

- GSK Medical Governance approval **is granted** (as described below),
- Ethics and/or IRB approval is obtained, if required, and
- Separate consent for treatment restart/rechallenge is signed by the subject

If GSK Medical Governance approval to restart/rechallenge subject with study treatment **is not granted**, then subject must permanently discontinue study treatment and may continue in the study for protocol-specified follow up assessments,

Rechallenge Following Liver Stopping Events that are Possibly Related to Study Treatment

Following drug-induced liver injury, **drug rechallenge is associated with a 13% mortality across all drugs in prospective studies** [Andrade, 2009]. Clinical outcomes vary by drug, with nearly 50% fatality with halothane readministered within one month of initial injury. However, some drugs seldom result in recurrent liver injury or fatality. Risk factors for a fatal drug rechallenge outcome include:

- Hypersensitivity [Andrade, 2009] with initial liver injury (e.g. fever, rash, eosinophilia)
- jaundice or bilirubin >2xULN with initial liver injury (direct bilirubin >35% of total)
- subject currently exhibits severe liver injury defined by: ALT ≥3xULN, bilirubin ≥2xULN (direct bilirubin >35% of total), or INR≥1.5
- serious adverse event or fatality has earlier been observed with drug rechallenges [Hunt, 2010; Papay, 2009]
- evidence of drug-related preclinical liability (e.g. reactive metabolites; mitochondrial impairment [Hunt, 2010].

Rechallenge refers to resuming study treatment following drug induced liver injury (DILI). Because of the risks associated with rechallenge after DILI this should only be considered for a subject for whom there is compelling evidence of benefit from a critical or life-saving medicine, there is no alternative approved medicine available, and a benefit:risk assessment of rechallenge is considered to be favourable.

Approval by GSK for rechallenge with study treatment can be considered where:

- Principal Investigator (PI) requests consideration of rechallenge with study treatment for a subject who is receiving compelling benefit with study treatment that exceeds risk, and no effective alternative therapy is available.
- Ethics Committee or Institutional Review Board approval for rechallenge with study treatment must be obtained, as required.

- If the rechallenge is approved by GSK Medical Governance in writing, the subject must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the rechallenge with study treatment. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by GSK.
- Subjects approved by GSK Medical Governance for rechallenge with study treatment must return to the clinic twice a week for liver chemistry tests until stable liver chemistries have been demonstrated and then standard laboratory monitoring may resume as per protocol.
- If after study treatment rechallenge, subject meets protocol-defined liver chemistry stopping criteria, study treatment should be permanently discontinued.
- GSK Medical Monitor, and the Ethics Committee or Institutional Review Board as required, must be informed of the subject's outcome following study treatment rechallenge.
- GSK to be notified of any adverse events, as per Section 7.2.

Restart Following Transient Resolving Liver Stopping Events Not Related to Study Treatment

Restart refers to resuming study treatment following liver stopping events in which there is a clear underlying cause (other than DILI) of the liver event (e.g. biliary obstruction, pancreatic events, hypotension, acute viral hepatitis). Furthermore, there should be no evidence of alcoholic hepatitis or hypersensitivity, and the study treatment should not be associated with HLA markers of liver injury.

Approval by GSK for study treatment restart can be considered where:

- Investigator requests consideration for study treatment restart if liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3xULN).
- Restart risk factors (e.g. fever, rash, eosinophilia, or hypersensitivity, alcoholic hepatitis, possible study treatment-induced liver injury) or study treatment has an HLA genetic marker associated with liver injury (e.g. lapatinib, abacavir, amoxicillin/clavulanate) are reviewed and excluded.
- Ethics Committee or Institutional Review Board approval of study treatment restart must be obtained, as required.
- If restart of study treatment is approved by GSK Medical Governance in writing, the subject must be provided with a clear description of the possible benefits and risks of

study treatment administration, including the possibility of recurrent, more severe liver injury or death.

- The subject must also provide signed informed consent specifically for the study treatment restart. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by GSK.
- Subjects approved by GSK Medical Governance for restarting study treatment must return to the clinic once a week for liver chemistry tests until stable liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.
- If after study treatment re-start, subject meets protocol-defined liver chemistry stopping criteria, follow usual stopping criteria instructions.
- GSK Medical Monitor, and the Ethics Committee or Institutional Review Board as required, must be informed of the subject's outcome following study treatment restart.
- GSK to be notified of any adverse events, as per Section 7.2.

References:

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